U.PORTO

DOUTORAMENTO

METABOLISMO – CLÍNICA E EXPERIMENTAÇÃO

Bone Metabolism And Body Composition After Bariatric Surgery

Fernando Miguel da Silva Mendonça

D

2026

BONE METABOLISM AND BODY COMPOSITION AFTER BARIATRIC SURGERY

METABOLISMO ÓSSEO E COMPOSIÇÃO CORPORAL APÓS CIRURGIA BARIÁTRICA

CANDIDATO

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DOUTORAMENTO

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2026

~

DISSERTAÇÃO DE CANDIDATURA AO GRAU DE DOUTOR

EM METABOLISMO - CLÍNICA E EXPERIMENTAÇÃO

APRESENTADA À FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

ARTIGO 48º, PARÁGRAFO 3º:

“A FACULDADE NÃO RESPONDE PELAS DOUTRINAS EXPENDIDAS NA DISSERTAÇÃO”

REGULAMENTO DA FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

DECRETO-LEI Nº 19337 DE 29 DE JANEIRO DE 1931

FAZEM PARTE INTEGRANTE DESTA TESE OS SEGUINTES TRABALHOS:

1. Mendonça F, Soares R, Carvalho D, Freitas P. The Impact of Bariatric Surgery on Bone Health: State of the Art and New Recognized Links. Horm Metab Res. 2022 Mar;54(3):131-144

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Aos meus pais

À Anabela

À minha irmã Ana Isabel

À minha família e amigos

A todos aqueles que me apoiaram nesta jornada

AGRADECIMENTOS

Esta tese que está prestes a ler é o resultado de mais de 8 anos de trabalho, o que corresponde a um quarto de todo o meu tempo de vida à data da sua entrega. Costumo dizer humoristicamente à Prof. Raquel Soares (a minha mãe científica) que sou provavelmente o *Dux* atual do seu programa doutoral. Mas a realidade é que neste período, iniciei e concluí o meu internato de formação específica enquanto travei uma batalha para manter à tona este projeto clínico durante a pandemia COVID-19. Ao insistir num trabalho prospetivo com mais de 160 doentes e num *follow-up* de dois anos (para apimentar ainda mais as coisas, porque o resto ainda não era emoção suficiente!), aprendi também da pior maneira porque que é que os doutoramentos clínicos tendem estatisticamente a ser mais prolongados no tempo. Olhando "pelo retrovisor", chego à conclusão de que o projeto BARIATRIC BONE só se materializou neste documento graças à minha teimosia e a uma dose considerável de loucura. O facto de ter fornecido o meu contacto telefónico pessoal a todas as doentes incluídas (para desprazer da minha namorada) ilustra isso mesmo (a ULS de São João não atribui telemóveis aos internos). Apesar de tudo, penso que essa decisão foi fundamental para salvar o projeto porque estabeleceu um vínculo entre as doentes e a equipa médica, permitindo minimizar perdas de *follow-up*. Como deve calcular, tal "central telefónica ambulante" deu origem a várias histórias caricatas, que incluíram pedidos de consulta para "infiltrar o meu filhinho muito gordo na lista para cirurgia!" e também "muitas desculpas meu querido, não vou poder ir ao exame porque fui agora mesmo atropelada por uma ambulância à frente do São João!".

O tempo ajudar-me-á a compreender a real magnitude do que foi conseguido com o projeto BARIATRIC BONE e talvez me clarifique (ou provavelmente não!) o porquê de um indivíduo racional sem patologia psiquiátrica diagnosticada se submeter de forma voluntária às tormentas que um projeto doutoral acarreta. Apesar da maioria dessas tormentas terem recaído sobre a minha pessoa, este esteve longe de ser um *one man show*. Aquilo que mais me orgulho neste projeto não é este documento, os seus resultados ou os artigos científicos que dele resultaram. É o facto de uma única pessoa ter sido suficiente para motivar centenas de outras pessoas (doentes, administrativos, auxiliares, enfermeiros, médicos, alunos e investigadores) em torno de um objetivo comum. Estarei eternamente grato a todas essas pessoas e, por isso mesmo, lhes dedico a minha sincera homenagem.

Começo por agradecer às doentes incluídas, que amavelmente disponibilizaram o seu tempo para a realização dos exames (como as densitometrias ósseas e colheitas de urina de 24h) associados a este estudo. Sem o seu contributo, este trabalho seria apenas uma utopia.

Não posso obviamente deixar de agradecer às minhas orientadoras, as Prof. Doutoras Paula Freitas e Raquel Soares (também arguente e orientadora da minha tese de Mestrado, respetivamente) pelo acompanhamento prestado a este trabalho e pelas ideias/ soluções encontradas em alguns momentos críticos do projeto. Agradeço também à Prof. Paula pelo papel determinante que apresentou no meu período de formação clínica enquanto interno (e por ser, desta vez, orientadora em vez de arguente!) e à Prof. Raquel por ter sido a primeira pessoa a acreditar em mim do ponto de vista científico. Espero ter estado à altura das expectativas de ambas.

Não posso também deixar de agradecer o incansável apoio da equipa de Bioquímica da Faculdade de Medicina da Universidade do Porto, em particular da Prof. Doutora Carla Luís e da Dra. Ilda Rodrigues, responsáveis pelo tratamento de centenas de amostras sanguíneas que foram essenciais para o doseamento de alguns dos parâmetros avaliados neste trabalho e também pela recolha de alguns dos tubos em dias mais difíceis. A importante colaboração das alunas Beatriz Silva, Joana Alves, Maria Beatriz Fonseca, Beatriz Pinto, Joana Barbosa e Luísa Couto não será também esquecida. Por fim, agradeço à Prof. Doutora Liliana Carvalho que, para além de ter um papel ativo no grupo laboratorial deste projeto, desempenhou um papel muito importante esclarecimento e resolução de assuntos administrativos relacionados com este projeto doutoral.

Queria também deixar um obrigado a toda a equipa do Centro de Responsabilidade Integrada em Obesidade, em especial aos colegas de Endocrinologia (Prof. Paula Freitas, Dra. Ana Varela, Dra. Selma Souto, Dr. Jorge Pedro, Dra. Diana Festas, Prof. Doutora Eva Lau, Dr. Pedro Rodrigues) e também aos colegas nutricionistas Hugo Canelas, Diva Melim e Prof. Flora Correia com quem tive o prazer de trabalhar diretamente. Os vossos registos clínicos foram fundamentais para a construção da base de dados que deu origem aos resultados que apresentarei de seguida. Um agradecimento especial à Dra. Selma Souto, que para além dos seus registos, contribuiu também com a sua importante tutoria durante o meu internato médico.

Foram também vários os elementos da equipa de Medicina Nuclear que me apoiaram neste percurso e facilitaram agendamentos de densitometrias ósseas, sem os quais não conseguiria respeitar os timings de seguimento deste projeto. Por esse motivo, aos Prof.

Doutores Ana Rita Fernandes, Jorge Pereira, Teresa Faria, mas também a todos os técnicos de Medicina Nuclear envolvidos, o meu sincero obrigado.

A minha gratidão estende-se à fantástica equipa de técnicos de colheitas de sangue da ULS São João, em particular às técnicas Sónia Vieira e Sandra Carvalho que, com a coordenação do Dr. Altin Ndrio e do Prof. Doutor Tiago Guimarães, sempre foram um elo essencial na engrenagem de todo este projeto. Estendo também este agradecimento à equipa de administrativos das colheitas pelos múltiplos pedidos de reagendamento de análises por férias nas Maldivas, amnésia seletiva para a data da colheita, ou urina não colhida por cataménios abundantes (várias doentes chegaram mesmo a reportar que não iam entregar chá de frutos vermelhos nas colheitas… E assim se destrói o chá favorito de uma pessoa!).

Às enfermeiras Carmo e Anabela da equipa de Endocrinologia, exemplo de resiliência e profissionalismo, agradeço pelas colheitas sanguíneas "surpresa" quando tal não era possível na central de colheitas. Estendo esse agradecimento também à Enfermeira Ema do Hospital de Dia de Endocrinologia, essencial para agilizar a colheita de tubos com amostras sanguíneas neste espaço.

Ao Professor Doutor João Sérgio Neves e à Dra. (quase professora) Ana Rita Leite o meu obrigado pelo importante apoio no tratamento estatístico da gigantesca base de dados que resultou deste projeto. Agradeço também ao Prof. João Sérgio pelos *inputs* que foi dando na fase inicial do projeto e que contribuíram de forma determinante para a sua melhoria.

Estendo os agradecimentos aos meus "irmãs e irmãos de armas" nesta aventura que, tal como os dois "estatísticos", podiam muito bem ser conhecidos por "Lesados do BARIATRIC BONE". Às minhas alunas de tese de Mestrado (que agora já são médicas), as Dras. Pietra Soares e Mafalda Maia, agradeço o rigor, dedicação e as várias tardes passadas comigo a fazer dezenas de chamadas telefónicas e a montar bases de dados enquanto se bebia café de máquina e comia rebuçados e chocolate *Milka* do bar do hospital (o nosso SNS sabe sempre como promover estilos de vida saudáveis!). Estendo esse agradecimento à equipa atual do projeto, que continua comigo a acompanhar as doentes incluídas até aos 10 anos após a cirurgia. Ela é constituída pelos meus internos os Drs. João Teixeira e Hugo Marinho e pela minha aluna de Mestrado Inês Figueiredo. Obrigado a todos vós por manterem este projeto vivo e pelo vosso profissionalismo, empatia e empenho que dedicam a esta causa.

Um obrigado a todos os colegas do serviço de Endocrinologia que me ajudaram esporadicamente na recolha de amostras sanguíneas durante os meus períodos de

férias e aos que, de uma forma ou de outra, me motivaram a continuar o desenvolvimento do projeto até esta fase. Destaco entre eles a Dra. Telma Moreno que foi um importante elemento na recolha de amostras na fase inicial do projeto.

Termino como uma nota mais pessoal. Um projeto doutoral é geralmente mais penalizador para aquelas pessoas únicas a quem decidimos dedicar o nosso tempo extralaboral, o tempo de vida mais valioso de todos. Enquanto doutorandos, gostamos de acreditar que podemos encontrar o equilíbrio num mundo desequilibrado e que, se tentarmos muito, conseguimos fazer tudo e estar em todo o lado ao mesmo tempo. Na verdade, nunca tive esse tipo de superpoderes. Por isso, não posso deixar de sublinhar o papel central das pessoas que, não tendo estado diretamente envolvidas no projeto, foram também fundamentais para a sua conclusão.

Agradeço aos meus pais pelos valores transmitidos e por me ensinarem a apreciar a beleza das pessoas simples, genuínas e com carácter. O seu sentido de trabalho e resiliência fazem parte do ADN deste projeto. Obrigado pela sua presença constante em todos os momentos importantes.

À minha namorada Anabela, uma força da natureza que resistiu a um internato, uma pandemia e um doutoramento, e que acompanhou de perto o desenvolvimento deste projeto, obrigado pelo apoio moral e emocional e pelo seu sorriso redentor.

Aos meus avós maternos, figuras também centrais na minha educação, agradeço pela experiência de vida partilhada, pela sabedoria e pelas conversas ao fim de semana (que acabam quase sempre por se tornar numa consulta médica ao domicílio graças às queixas álgicas difusas da minha avó, que estranhamente desaparecem sempre em dias de festa!);

À minha irmã Ana Isabel (a minha mãe Maria Albertina não lhe chamou Vanessa, o que foi uma tremenda oportunidade perdida para a praxar ainda mais com a música dos Humanos que ela detesta), agradeço pelo honestidade, companheirismo e alegria.

À minha restante família, conhecida por festejar sempre com uma sobremesa por pessoa (daqui a uns tempos talvez venha a precisar dos serviços cirúrgicos do CRIO!), agradeço pelos momentos de lazer e partilha.

Termino com um agradecimento a todos os meus amigos, personagens também muito importantes para a manutenção da sanidade mental necessária ao longo desta travessia no deserto, dos quais destaco Gabriel Conceição, Bruno Carvalho e Catarina Cruz.

Muito obrigado a todos!

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FOREWORD

This dissertation is divided into six main chapters:

Chapter 1 presents an introduction to the thesis. In the first part, a review article will address the impact of bariatric surgery (and its main techniques) on bone health, including aspects related to bone mineral density variation after surgery, fracture risk, the role of nutritional and hormonal players, among others. In the second part, current knowledge on body composition changes induced by bariatric surgery is presented. The concept of sarcopenic obesity will also be clarified.

Chapter 2 focuses on the main objectives of this project.

Chapter 3 encompasses the results of the investigations undertaken by the doctorate student, displayed in the form of published or submitted articles.

Chapter 4 provides a global discussion of the main findings, integrating them with previously published data. The possible implications of these findings for clinical practice will also be addressed.

Chapter 5 summarizes the main conclusions of this dissertation and outlines future perspectives.

Chapter 6 presents the references of the articles used to support the introduction and discussion.

ABSTRACT

RESUMO

Resumo

Introdução: A cirurgia bariátrica (CB) é uma opção terapêutica amplamente utilizada para doentes com obesidade grave, proporcionando melhorias substanciais não só no peso, mas também em várias comorbilidades associadas a esta doença. Apesar dos seus benefícios incontestáveis, o possível impacto negativo da perda rápida de peso no metabolismo ósseo tornou-se uma temática muito em voga, sobretudo na última década. A deterioração óssea após CB resulta de vários fatores, como a redução da absorção de cálcio e vitamina D (com hiperparatiroidismo secundário associado), a diminuição da carga mecânica e alterações nos níveis de hormonas adipocitárias e gastrointestinais. Apesar de existir cada vez mais evidência dos efeitos deletérios tanto da gastrectomia vertical (SG) como do bypass gástrico em Y-de-Roux (RYGB), são escassos os estudos prospetivos que comparam diretamente estas técnicas, apresentando, na maioria dos casos, menos de 70 doentes e apenas um ano de seguimento. Para além disso, a CB provoca alterações significativas na composição corporal, levando não só à redução de massa gorda, mas também de massa magra (incluindo tecido muscular). A interação osso-músculo e o conceito emergente de obesidade sarcopénica (OS) — combinação de deterioração muscular e elevada adiposidade — realçaram a importância da variação da massa magra após CB e das respetivas implicações metabólicas.

Objetivo: Esclarecer o impacto da cirurgia bariátrica (e das suas duas principais técnicas) nos marcadores de metabolismo ósseo, densidade mineral óssea (BMD) e composição corporal após a cirurgia.

Métodos: Neste projeto foram usadas duas abordagens e populações distintas: **A)** Estudo retrospetivo unicêntrico em que se avaliou a prevalência de hiperparatiroidismo secundário (SHPT) antes e depois da CB, os seus preditores e particularidades. Selecionaram-se consecutivamente 1431 doentes avaliados no Centro de Responsabilidade Integrado de Obesidade (CRIO) da ULS São João, submetidos a CB

entre janeiro/2010 e junho/2017, com seguimento mínimo de um ano até quatro anos. **B)** Estudo de coorte prospetiva: incluíram-se 162 mulheres com obesidade submetidas a RYGB ou SG (≥40 anos), entre novembro/2019 e dezembro/2022, no mesmo centro. Foram analisados: **1)** impacto da técnica cirúrgica (RYGB *vs* SG) **e 2)** comparação de mulheres pré- e pós-menopáusicas quanto à variação da BMD, composição corporal avaliada por densitometria óssea, níveis séricos de FGF-21, FGF-23 e marcadores ósseos (osteocalcina, telopéptido C [CTX]) nos dois primeiros anos pós-CB; **3)** comparação entre grupos de doentes com diferentes graus de gravidade de OS segundo o consenso ESPEN/EASO-2022 (n = 140) nos primeiros 12 meses após cirurgia. Nestes 3 estudos, foram avaliados parâmetros clínicos, densitométricos e bioquímicos antes e após CB, tendo-se utilizado a variação dos parâmetros para comparação entre os grupos.

Resultados: A prevalência de SHPT foi de 24,9 % antes da cirurgia, 11,2 % um ano depois e 21,3 % quatro anos depois. Um ano após a cirurgia, a banda gástrica (LAGB) apresentou a maior prevalência de SHPT (19,4 % *vs* RYGB 12,8 % *vs* SG 5,3 %). Aos quatro anos após CB, o RYGB teve a maior prevalência de SHPT (27,0 %), seguido de LAGB (13,2 %) e SG (6,9 %). Maior IMC, idade avançada, níveis reduzidos de vitamina D e RYGB foram preditores independentes de SHPT um ano após CB. Aos quatro anos, apenas o RYGB se manteve preditor de SHPT. Relativamente à coorte prospetiva (162 mulheres), 99 (61,1 %) foram submetidas a RYGB e 63 (38,9 %) a SG. A densidade mineral do fémur total diminuiu significativamente um e dois anos após CB, com queda mais acentuada da DMO no RYGB. Dois anos após CB, o RYGB promoveu maior redução da DMO no colo femoral. O RYGB implicou maior perda de massa gorda um e dois anos após, sem diferenças na redução de massa magra. Osteocalcina e CTX aumentaram mais no RYGB em ambos os momentos. O RYGB foi preditor de redução de BMD no fémur total, colo femoral e coluna lombar dois anos após cirurgia mesmo após ajuste para a idade.

Embora nem o FGF21 ou FGF23 tenham sido preditores da variação da DMO dois anos após a cirurgia, observou-se uma maior proporção de pacientes submetidos a SG com níveis indetetáveis de FGF-21 no início do estudo [88,9 *vs* 55% (p=0.001)], verificando-se uma ocorrência semelhante na variação dos seus níveis séricos um e dois anos após a CB. Os níveis séricos de FGF-23 previamente à cirurgia eram mais elevados entre os pacientes que aguardavam SG (534,5 *vs* 335,6pg/mL, p=0.003). Embora o RYGB tenha induzido maiores variações positivas nos níveis de FGF-23 um (+116,7 *vs* +32,7 pg/mL) e dois anos (+164,4 *vs.*+93,8 pg/mL) após a cirurgia, não foram registadas diferenças estatisticamente significativas entre as técnicas cirúrgicas. Mulheres pós-menopáusicas apresentaram maior prevalência de DM2, hipertensão e osteopenia. Dois anos após CB, apresentaram maior decréscimo do conteúdo mineral ósseo, maior perda de BMD no fémur total e corpo inteiro, e maior redução de massa magra total e dos membros superiores. Antes da CB, a prevalência global de OS era de 89,3 %, caindo para 2,9 % após CB. O grupo 1 (OS mais grave) tinha mais massa gorda total, troncular e dos membros inferiores, enquanto apresentava menor massa magra basal. Um ano pós-CB, este grupo perdeu mais peso, IMC e massa gorda, mas não apresentou maior diminuição de massa magra. As taxas de remissão de comorbilidades foram substanciais em todos os grupos, mas mais marcadas no grupo 1. A prática de exercício físico aumentou após CB.

Conclusões: O RYGB mostrou maior impacto no metabolismo ósseo e na composição corporal que o SG, com efeitos mais marcados no fémur e na redução de massa gorda. As mulheres pós-menopáusicas perderam mais massa magra e densidade mineral óssea após CB (apresentando perda ponderal semelhante), sublinhando a necessidade de estratégias pós-cirúrgicas individualizadas, incluindo suporte nutricional otimizado e vigilância da saúde óssea. Apesar da preocupação inicial de que os mecanismos hipoabsortivos poderiam intensificar a perda muscular, os doentes com OS mais grave perderam mais massa gorda, mas apresentaram a menor redução de massa magra. A

prevalência de SHPT é maior antes e quatro anos após CB do que um ano depois, o que levanta questões sobre a eficácia, a longo prazo, dos planos de suplementação de vitamina D, sobretudo em doentes submetidos a RYGB.

Abstract

Introduction: Bariatric surgery (BS) represents nowadays a widely used therapeutic option for patients with severe obesity, presenting substantial improvements not only in weight but also in several obesity-associated comorbidities. Despite its undisputed benefits, the putative negative impact of rapid weight loss in bone metabolism has become a hot topic mainly during the last decade. Bone deterioration occurring after bariatric surgery results from multiple players such as reduced calcium and vitamin D absorption (with associated secondary hyperparathyroidism), mechanical unloading and changes in adipocyte and gastrointestinal hormone levels. Despite the increasing body of evidence to support the deleterious effects on bones of both sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB), the number of prospective studies directly comparing these techniques are scarce and have a limited number of patients (usually less than 70) during a follow-up period of one year in most cases. In addition, BS exerts significant changes in body composition, leading not only to a reduction in fat mass but also in lean tissue (including muscle). Bone-muscle crosstalk and the emerging concept of sarcopenic obesity (SO), characterized by the confluence of muscle deterioration and high adiposity, have drawn attention to variations in lean mass after variation after BS and its possible implications to metabolic health.

Purpose: To clarify the impact of bariatric surgery (and its two main techniques) on bone metabolism markers, bone mineral density (BMD) and body composition after surgery.

Methods: For this project, two different populations and approaches were used: **A)** A single-center retrospective study was conducted to evaluate the prevalence of secondary hyperparathyroidism (SHPT) before and after BS, its predictors and particularities. To that end, 1431 patients were consecutively selected during the

preoperative evaluation by the Integrated Responsibility Center for Obesity (CRIO) in ULS São João, being submitted to BS between January 2010 and June 2017 and followed for at least one year and up to four years.

B) A prospective cohort study of 162 female patients with obesity submitted to RYGB or SG was also conducted. These individuals presented ≥40 years-old and were consecutively selected between November/2019 and December/2022 in the same outpatient setting from the previous ones. This pool of 162 female patients were divided in groups that led to the following investigations: **1)** comparison of the impact of the surgical technique (RYGB *vs* SG) and **2)** comparison of pre- *vs* postmenopausal women at the time of surgery on the variation of BMD, body composition evaluated by Dual-energy X-ray Absorptiometry, FGF21 and FGF23 serum levels, and bone metabolism markers [such as osteocalcin and C- terminal telopeptide (CTX)] and during the first two years after BS; **3)** comparison of groups of patients (only 140 of the 162 were studied) with varying degrees of sarcopenic obesity (SO) severity, during the first 12 months after BS, calculated considering the consensus issued by ESPEN and EASO in 2022. Evaluations of clinical, densitometric and biochemical parameters were conducted before and after BS, and the variation was used for comparative purposes

Results: The overall prevalence of SHPT was 24.9% before surgery, 11.2% 1 year after surgery and 21.3% 4 years after surgery. Patients submitted to laparoscopic adjustable gastric banding (LABG) had the highest prevalence of SHPT 1 year after surgery (19.4%; *vs* RYGB 12.8% *vs* SG 5.3%). Four years after surgery, RYGB had the highest prevalence of SHPT (27.0%), followed by LAGB (13.2%) and SG (6.9%). Higher body mass index and age, decreased levels of vitamin D and RYGB seem to be independent predictors of SHPT 1 year after surgery. The only independent predictor of SHPT 4 years after surgery was RYGB. Of the 162 included patients in the prospective cohort, 99 (61.1%) underwent RYGB and 63 (38.9%) SG. Total femur BMD significantly decreased one and two years after BS, with a steeper reduction in the RYGB group. Two years after

surgery, RYGB led to a greater BMD decline in femoral neck. RYGB group also presented more fat loss at both time points, with no differences in lean mass reduction at one and two years after surgery. Osteocalcin and CTX increased at both time points, with a significantly higher increase in RYGB group. RYGB was predictor of BMD reductions in total femur, femoral neck and lumbar spine, even after adjusting for age. Postmenopausal patients showed a higher prevalence of T2D, hypertension and osteopenia. Two years after BS, postmenopausal patients revealed to have a steeper decrease in bone mineral content, a higher loss of total femur and whole-body bone mineral density. Postmenopausal patients presented a greater decrease in total body lean mass and arms lean mass. Although neither FGF21 nor FGF23 predicted BMD variation 2 years after surgery, there was a greater proportion of patients submitted to SG with undetectable levels of FGF-21 at baseline [88.9 *vs* 55% (p=0.001)], with similar occurrence observed in the variation of its serum levels at one and two years after BS. FGF-23 serum levels at baseline were higher among patients awaiting SG (534.5 vs 335.6pg/mL, p=0.003). Although RYGB induced greater positive variations of FGF-23 levels one (+116.7 vs +32.7pg/mL) and two years (+164.4 vs +93.8pg/mL) after surgery, there were no statistically significant differences between surgical techniques.

Before BS, SO prevalence in the overall sample was 89.3%, decreasing to 2.9% after BS. Group 1 (presenting more severe SO) had more body fat mass, total, trunk and leg fat at baseline and a significantly lower total skeletal muscle mass. One-year post-BS, group 1 presented more weight, BMI reduction and lost more fat mass, but not total lean mass. Remission rates for comorbidities were substantial among all groups, but more marked among patients within group 1. Engagement in physical exercise of any kind has increased post-BS.

Conclusions: RYGB showed a greater impact in bone metabolism and body composition than SG, with noticeable effects in the hip bone and fat mass reduction. Postmenopausal women undergoing BS experience a more significant loss of lean mass

and bone mineral density (with a similar weight loss). These findings underscore the necessity for tailored post-surgical strategies, including optimized nutritional support and vigilant bone health monitoring, to mitigate potential adverse effects. Despite concerns about hypoabsorptive mechanisms potentially worsening muscle loss, patients with the most severe SO undergoing BS lost more fat mass while experiencing the smallest reduction in total lean mass. The prevalence of SHPT is higher before and 4 years after BS than 1 year after surgery. This fact raises some questions about the efficacy of the implemented follow-up plans of vitamin D supplementation on the long term, mainly among patients submitted to RYGB.

CHAPTER 1

INTRODUCTION

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The Impact of Bariatric Surgery on Bone Health: State of the Art and New Recognized Links

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Key words
bariatric surgery, bone, sleeve gastrectomy, Roux-en-Y gastric bypass, fractures

received 23.11.2021
accepted after revision 26.01.2022

Bibliography
Horm Metab Res 2022; 54: 131–144
DOI 10.1055/a-1767-5581
ISSN 0018-5043
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Abstract

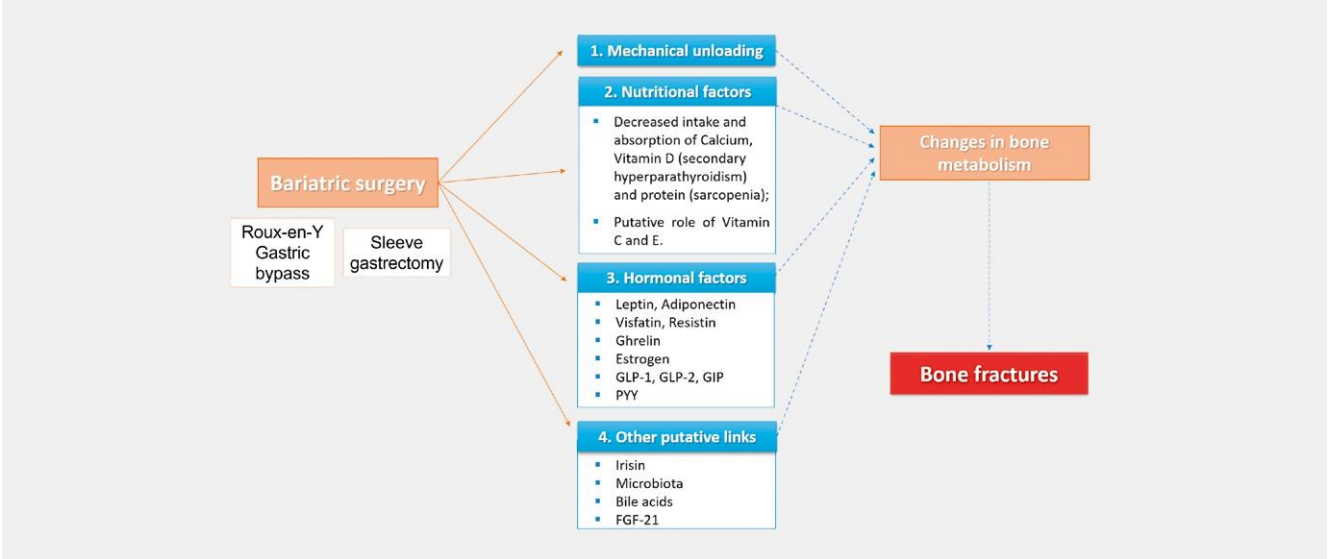
Bariatric surgery (BS) is the most effective therapy for severe obesity, which improves several comorbidities (such as diabetes, hypertension, dyslipidemia, among others) and results in marked weight loss. Despite these consensual beneficial effects, sleeve gastrectomy and Roux-en-Y gastric bypass (the two main bariatric techniques) have also been associated with changes in bone metabolism and progressive bone loss. The objective of this literature review is to examine the impact of bariatric surgery on bone and its main metabolic links, and to analyze the latest findings regarding the risk of fracture among patients submitted to bariatric surgery.

Introduction

Obesity is a preventable global health problem that continues to grow at an alarming rate [1]. According to the World Health Organization, in 2016, almost 2 billion adults were overweight and 650 million were obese [2]. Projected estimates from 2017 show that in 2030, obesity levels could reach huge proportions in some countries, such as the United States, Mexico, and the United Kingdom, where respectively 47, 39, and 35 % of the population is believed to be affected by this chronic disease [3]. These data gain particular relevance after acknowledging that obesity is related with multiple associated conditions, such as type 2 diabetes [4], hypertension [5], dyslipidemia [6], obstructive sleep apnea, cardiovascular disease, cancer, and increased mortality [7–9]. The management of this disease and its associated complications has evolved during the last decade [10], with an increased awareness for the long-term benefits of a more definitive approaches, such as bariatric surgery [11, 12]. These benefits (which include durable weight loss, diabetes remission, and the amelioration of multiple cardiovascular risk factors and other comorbidities) led to a progressive increase in the number of surgeries performed worldwide [13, 14].

Despite these advantages, one possible side effect of surgical procedures is their negative impact on bone health, an important issue that received more attention during the last decade [15, 16]. The mechanisms that are responsible for bone deterioration after bariatric surgery encompass diminished mechanical loading, malabsorption (calcium and vitamin D, among other nutrients) and altered gastrointestinal and adipocyte hormone levels [17].

Accordingly, the objective of this narrative review is to analyses the impact of bariatric surgery on bone metabolism, focusing mainly on the two most performed procedures worldwide [sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB)] (▶ **Fig. 1**). The review then proceeds to present the main players in this intricate relationship and to explore new recognized connections, based on recent data. The main techniques to measure bone mineral density



▶ **Fig. 1** Schematic presentation of the connections between bariatric surgery and bone metabolism. GLP-1: Glucagon-like peptide 1; GLP-2: Glucagon-like peptide 2; GIP: Gastric inhibitory polypeptide; PYY: Peptide YY; FGF-21: Fibroblast growth factor 21.

and predict fracture risk are also discussed, as well as the risk of a fracture occurring after bariatric surgery.

Measuring the Impact of bariatric surgery on bone mass and fracture risk

Several imagiological and analytical tools have been applied, mainly during the last decade, to understand how obesity and bariatric surgery affects bone metabolism. Most of them used dual-energy X-ray absorptiometry (DXA), which is a quantitative non-invasive technique that is the standard reference method for measuring BMD. DXA is commonly used to diagnosis and monitor osteoporosis, however it can also have other applications, such as in evaluating whole body composition [18]. Despite being extensively used as the main imagery for evaluating bone (even among obese individuals), it does, however, have various limitations. Up until recently, the tables of DXA scanners were only able to support a maximum weight of 136-160 kg, depending on the machine used. Despite the fact that newer models can support heavier weights (up to 205 kg), the problem is that sometimes tables are not wide enough to accommodate some severely obese patients [15]. In addition, the precision of DXA scans declines with higher BMI and excessive fat accumulation around bones, which could lead to unpredictable errors in DXA evaluation of up to 20 %. This fact explains the increased difficulty in obtaining and interpreting measurements from axial sites (lumbar spine, hip) when compared with those from peripheral ones (such as radius or tibia). Other problems that lead to imprecisions include differential positioning of adipose abdominal panniculus and the presence of vertebral fractures, which can also contribute to erroneous BMD values [19]. The accuracy of BMD is also affected by significant weight loss, which is a recurrent problem among this particular population who is submitted to bariatric surgery. This problem seems to be related with an alteration in the distance between X-ray source and the bone, owing to the diminished interposition of fat (which can change the evaluation of bone area, while calculating areal BMD or bone mineral content) [20]. Another handicap of DXA is that it can only measure two different tissues at the same time (for instance, soft tissue and bone) and when it measures body composition, a DXA scan tends to make assumptions about fat/lean tissues ratios to reveal the densities of three different tissues (lean tissue, fat, and bone). These ratios can be flawed in cases of significant weight loss. Finally, different manufacturers of DXA machine (GE-Lunar, Hologic, Norland) employ distinct methods to determinate BMD and adipose tissue proportion, which makes it impossible to compare results obtained from machines with different brands [21].

Bearing in mind the limitations of the use of DXA in obese states, other methods for evaluating have been pursued. One of them is quantitative computed tomography (QCT), which is a three-dimensional technique that quantifies BMD in several sites, such as the hip, spine (axial QCT) [22] or forearm, proximal femur, and tibia (peripheral QCT - pQCT). The strengths of QCT are the ability to separate cortical and trabecular bone, the determination of 3D geometric parameters (such as cross-sectional area, dimensions, cortical thickness, trabecular structure), and enabling the technician to characterize the bone in more detail. This ultimately leads to a better understanding of bone-related anomalies associated with the risk of fracture [23]. This exam can even be recommended for specific groups to maximize the accuracy of the evaluation of bone features, namely: very large or small patients (e. g., those with obesity) and older patients with advanced degenerative disease of the lumbar spine, as well as in cases where high sensitivity is needed (corticosteroid or parathormone treatment). The limitations of QCT include a relatively higher dose of radiation when compared with DXA and a limited number of longitudinal studies have evaluated QCT's ability to predict fractures [24, 25]. A study by Yu

et al. compared the QCT and DXA measurements of 30 patients with morbid obesity who had been submitted to RYGB. This study found that both methods detected a 3 % lower incidence of BMD in the spine, but discordant measurements at the hip, with the detection of a larger decline in total BMD when the patient was evaluated with DXA (9 %), with negligible changes of total BMD at any site of the hip when measured with QCT (despite having a 3.0–4.5 % loss of trabecular bone). The results suggest that one of these two methods is probably affected by the presence of foreign objects, which prompts the need for further research in the area of bone evaluation in obese/bariatric states [26].

The need to prevent bone fractures led the University of Sheffield to launch the fracture risk assessment tool (FRAX) in 2008, which provides country-specific algorithms to predict the 10-year probability of hip and major osteoporotic fracture (spine, hip, proximal humerus, and distal forearm) of a given patient. This tool evaluated seven different clinical risk factors that impact fracture risk, namely: previous fragility fracture, systemic glucocorticoid use, mother/father hip fracture, smoking, excess alcohol consumption, rheumatoid arthritis, and other causes of secondary osteoporosis. When added to age, sex, and BMI, these factors provide a 10-year fracture probability estimate that is independent of BMD [27]. This popular tool, which can be easily accessed through its website [28], includes the option to measure the BMD of femoral neck to refine the results. The FRAX estimate also helps physicians to decide whether to intervene therapeutically, although the various available guidelines differ with regards the treatment of cutoffs.

Another tool that can be incorporated optionally in the FRAX is the trabecular bone score (TBS) [29], which is a textural index that is associated with bone microarchitecture which analyses pixel gray-level variations in the DXA image of the lumbar spine. By so doing, TBS can distinguish differences in the 3-dimensional bone microarchitecture, even in 2-dimensional DXA evaluations with the same BMD levels. One finding that is independent of BMD is the fact that higher TBS values are correlated with stronger bone microstructure, whereas low values are correlated with a worse, fracture-prone microarchitecture [30]. The proposed TBS cutoffs for bone architecture among pos-menopausal women are: ˃1350 – normal; TBS between 1200 and 1350, which is consistent with partially-deteriorated bone microarchitecture; and TBS˂1200 – degraded bone microarchitecture. Limits for other groups of patients (such as male patients) are yet to be defined [31]. One of the main limitations of TBS is its lower accuracy for extreme levels of BMI, which is only being recommended for those patients who have a BMI of between 15–37 kg/m^2 [29]. When considering the BMI requirements for bariatric surgery, it is easy to understand that TBS has a limited range for application in these patients. Despite this fact, recent versions of the software are less impacted by excessive fat interposition, and at least two articles have applied this software among bariatric patients to predict fracture risk [32, 33].

The increase in bone turnover, which occurs in various pathological states (osteoporosis, among others), is associated with a decay of bone microarchitecture and with an increase in fracture risk that is independent of BMD [34]. This fact led to the increased popularity of the markers of bone turnover – biochemical agents evaluated in blood or urine. These products mirror bone metabolic activity and can be categorized as bone formation or bone absorption markers (▶ **table 1**) [35]. Even among bariatric patients, the most-used markers of bone formation are N-terminal pro-peptide of type 1 collagen (P1NP) and osteocalcin. In turn, the most-used markers of resorption are C-terminal telopeptide of type 1 collagen (CTX-1) and N-terminal telopeptide of type 1 collagen(NTX-1) [19].

▶ **table 1** Summary of the markers of bone formation and absorption, considering its specific physiological role on bone metabolism.

bone formation markers		**bone resorption markers**	
by-products of the synthesis of collagen	▪ Propeptides of type 1 collagen: – C-terminal: P1CP – N-terminal: P1NP	**Collagen degradation products**	▪ Telopeptides of type 1 collagen: – C-terminal: – CTX-1 and CTX-matrix metalloproteinases – N-terminal: NTX-1 ▪ Pyridinium crosslinks: – pyridinoline – deoxypyridonoline ▪ Hydroxyproline
Osteoblastic enzymes	▪ Bone-specific alkaline phosphatase (BSAP) ▪ Total alkaline phosphatase (weaker measure than BSAP – prone to interferences with liver diseases)	**Non-collagenous proteins**	▪ Bone sialoprotein
Matrix proteins	▪ Osteocalcin	**Osteocyte activity markers**	▪ Osteoprotegerin ▪ Receptor activator of nuclear factor kappa-B ligand (RANKL) ▪ Dickkopf-related protein 1
		Osteoclastic enzymes	▪ Cathepsin K ▪ Tartrate-resistant acid phosphatase

Bariatric surgery techniques and its impact on bone

Bariatric surgery has become the most effective option among obese patients to lose weight and for treating some of the related diseases. This surgery is indicated for those individuals with a BMI ≥ 40 kg/m², or those with BMI ≥ 35 kg/m² and comorbidities such as sleep apnea, dyslipidemia, hypertension, or type 2 diabetes mellitus. However, despite its positive effects, bariatric surgery can be detrimental for bone health, as shown by recent studies [36, 37]. Interestingly, the impact of bariatric surgery on bone appears to differ slightly, according to the surgical technique performed [38]. The two procedures that together account for more than 80 % of the performed bariatric surgeries worldwide are Roux-en-Y gastric bypass (RYGB) and Sleeve gastrectomy (SG). Accordingly, only these two procedures are addressed in this review.

The above-mentioned comorbidities lead to food restriction, malabsorption, and changes in the secretion of several gastrointestinal hormones, which can also impact on bone metabolism [39]. A meta-analysis in 2014, which focused on patients submitted to RYGB revealed a significant decrease in circulating calcium levels and a significant rise in PTH serum levels after surgery. Surprisingly, no difference in serum 25-OH vitamin D was found, although there was also a significant decrease in BMD after RYGB. With regards bone markers, there were significant increases in urinary and serum NTX and in bone-specific alkaline phosphatase (BSAP) [37]. A recent trial on bone marker variation after RYGB found similar results, with increased CTX-1, P1NP and BSAP 2 years after surgery [40]. Another study addressing bariatric type 2 diabetic patients found that there was a significant 280 % increase in osteoblast activity, and a significant decrease in BMD of lumbar spine (− 4.0 %, $p < 0.05$) one year after RYGB [41]. Several studies to date have focused on BMD variation after RYGB, where most of them used DXA measurements and detected a prominent areal Bone Mineral Density (aBMD) decline at the proximal femur during the first year after surgery, with decreases that range from 6 and 11 % [42]. This deterioration at the hip BMD (that is consistent among studies) can be overestimated by DXA, as articles addressing volumetric hip BMD by QCT found smaller declines [43, 44]. On the other hand, DXA assessments of the lumbar spine found that most of the worse aBMD values were after RYGB, albeit not with the same magnitude of the decline in hip aBMD. When considering all the studies addressing spinal BMD, it is evident that there appears to be a decrease in spine bone mass after RYGB which is underestimated by DXA when compared to QCT [42-45]. The appendicular skeleton is also affected, with diminished total and ultradistal radius aBMD detected 12 months after RYGB. The decline of tibial and radial volumetric BMD (vBMD) values is less marked than that observed at spine and hip, however, experiments with HR-QCT suggest that this method may underestimate vBMD variation in states of decreasing adipose mass [45, 46]. With regards the radius, the decrease in trabecular vBMD is responsible for the decline in total vBMD, which occurs due to changes within the cortical or both compartments, just as in the case of the tibia [43, 45, 47]. A recent study followed patients submitted to RYGB for seven years and found that BMD continued to decrease progressively, regardless of the bone site evaluated (hip, spine, radius, and tibia), and even after weight stabilization [48].

In addition, it is thought that SG also interferes in the production of multiple gastrointestinal hormones that regulate appetite, such as ghrelin [49]. As this technique is relatively new when compared with RYGB, it is not surprising that the data regarding its effects on the skeleton are still limited. Despite this fact, a recent systematic review and meta-analysis revealed that, after surgery, those patients submitted to SG presented an increase in serum calcium, serum 25-hydroxyvitamin D, and serum phosphate, while showing a decrease in serum Parathormone (PTH) levels. No change in serum alkaline phosphatase was seen after SG. Furthermore, a significant decrease in hip BMD and femoral neck BMD was reported. Interestingly, no changes in lumbar spine BMD were detected after surgery [50]. The authors of this recent review also pronounce on the observation that the magnitude of the reductions of BMD among those submitted to SG appear to be lower than those reported elsewhere for RYGB [37]. It is important to stress that the majority of all the articles included in the analysis had a follow-up period of 12 months, and that only one study presented a follow-up greater than one year (60 months) [50]. A recent observational study followed 48 patients submitted to SG for a period of four years. At year 4, the rates of bone loss were: 8.1 ± 5.5 % for the femur neck, 2.0 ± 7.2 % for the lumbar spine; 7.7 ± 6.4 % for the total hip, and 2.4 ± 5.5 % in for whole body BMI. This study, which also followed 47 individuals submitted to RYGB, concluded that bone loss at four years was comparable between procedures, although SG was associated with less bone deterioration for total hip BMD [51]. Another meta-analysis published in 2020 compared the changes in bone metabolism between SG and RYGB. It found that, among SG patients, the circulating levels of calcium were higher than those from RYGB, whereas those of phosphorus were lower. The alterations in 25-hydroxyvitamin D after SG were also less significant than those detected after RYGB. No differences in BMD were observed between the two groups regardless, of the area evaluated. 8 of the 13 studies included had a follow-up of 12 months, 1 of 6 months, and only 4 presented a follow-up longer than a year [52]. Another recent study addressing postmenopausal women found no significant differences between SG and RYGB in total and regional BMD after surgery. However, despite this fact, there was a clear decrease in the BMD of ribs and spine after surgery in both groups, which suggests that DEXA could have an important role postoperatively among high-risk women [53].

Despite the increasing body of evidence to support the deleterious effects on bones of both SG and RYGB, the currently-available data has several limitations. For instance, most of the studies are small, with an average population of fewer than 30 patients, with short follow-ups. For these reasons, further research is required to clarify not only the impact of SG on bone metabolism, but also the various other differences in outcomes between these two bariatric procedures [54].

Bone fractures and bariatric surgery

The most significant clinical consequence of bariatric surgery on the skeleton is bone fracture – a condition which is associated with increased morbidity and mortality [55]. Considering that bariatric

surgery (and malabsorptive procedures in particular) appears to be associated with increased bone loss, it became crucial to understand whether this resulted in the occurrence of fractures. The first steps were taken to clarify this relationship during the decade of 2010 to 2020 [56].

The first meta-analysis on the subject of bone fracture comprised five studies and it revealed that obese patients who have been submitted to bariatric surgery have a higher risk for all types of fracture when compared with non-surgical control individuals (note: this finding was even more pronounced in non-vertebral sites, such as the upper limbs). In addition, it was also found that subjects submitted to mixed procedures (with a component of restriction and another of malabsorption, such as RYGB) had a tendency to present increased fracture risk in comparison with those who underwent restrictive procedures [57]. Another systematic review consisted of 15 studies and was published the following year, revealing that bariatric surgery patients were associated with a higher risk of fracture when compared with individuals not submitted to surgery (but having a similar baseline weight). This fact was seen most often among those submitted to malabsorptive procedures. Three of these studies found that the fractures reported were mainly located in the lower limbs (involving the tarsal, metatarsal, and phalangeal bones). Interestingly, the meta-analysis of these trials did not exhibit an increased risk of fractures among bariatric surgery patients (contrary to what happened in purely observational studies) [58]. One of the explanations for this difference is the length of the follow-up period. For to be able to accurately evaluate the long-term fracture risk in such patients, it is essential that the length of follow-up periods is sufficiently long enough for fractures to occur. This becomes evident when comparing the results of observational studies which have more than five years follow-up [59–63] with the first observational study, which had a shorter follow-up [64]. The most recent meta-analysis addressing this issue was published at the end of 2020. It included 11 articles and states that, on average, bariatric patients had 1.41 times more fracture risk when compared with the non-surgical control group. Another relevant conclusion was that fracture risk after surgery was site-specific, affecting more the upper limbs, spine, and hip [65], which differs from the previous systematic review [58]. These divergences regarding fracture sites need to be clarified by carrying out with trials with longer follow-up periods (in order to maximize fracture occurrence), although this is an ideal scenario, which is difficult to achieve owing to increased follow-up losses as time progresses [66]. Finally, the risk of fracture associated with bariatric surgery continued to increase, even during the 5th postoperative year, when surgical-induced weigh loss is no longer occurs [65].

In conclusion, all the evidence to date seems to indicate that fracture risk after BS varies according to the procedure, with consistent evidence implicating that RYGB leads to an increased risk of clinically important fractures on one hand, while on the other hand, studies on SG found that the risk of fracture after this type of bariatric surgery is not greater than RYGB and could indeed potentially be even less. Despite these facts, more research is needed on fracture risk after SG. Other pertinent finding is that fracture risk appears to mainly occur two or more years after surgery, and then increases during the following years. Finally, fractures related with BS tend to occur at a much younger age than age-related fractures.

Our review thus highlights that fracture risk should be included as another factor for consideration when deciding whether to opt for BS, especially among older patients [56].

Bone loss after bariatric surgery: which factors need to be considered?

The detrimental effects of bariatric surgery on bone metabolism appear to have multiple etiologies which are discussed below in this section (▶ **table 2**).

Mechanical factors

One of the first mechanisms to be proposed as a link between bone loss and BS was mechanical unloading. For it is known that the skeleton adapts to the mechanical strain, leading to alterations in bone mass and microarchitecture when weight loading changes [67]. After being submitted to BS, body weight decreases up to 30 %, and this lower mechanical load can contribute to reduced bone formation, augmented bone resorption, and decreased BMD [16]. These effects seem to be mediated, at least partially, by the increased secretion by osteocytes of sclerostin – a negative regulator of bone formation [68]. However, mechanical factors cannot be cited as the cause of the continued loss of bone mass, despite weight stabilization [47], or even for altered bone architecture after BS in non-loading-bearing bone sites [61]. This gap can be partially filled by factors which are related to nutritional status.

Nutritional factors

After BS, there is a reduction of the intake of various nutrients which have a crucial role in maintaining bone mass, such as proteins, calcium, and vitamin D. This diminished intake is also aggravated by malabsorption issues which arise after surgery (mainly after RYGB, but also after SG), which thus paves the way for alterations in bone metabolism and for presumably related fractures [19, 21]. These post-surgical nutritional factors can also exacerbate pre-existing alterations in phosphocalcium metabolism (such as vitamin D deficiency), which further contributes to the development of secondary hyperparathyroidism (SHPT) [69]**.** As a matter of fact, Vitamin D insufficiency has been reported before surgery in up to 80 % of bariatric patients. In addition, several studies had demonstrated that, despite being supplemented, patients presented calcium and vitamin D levels that were usually below or in the lower end of the normal range after surgery [70]. Previous data revealed that patients with stable or increased vitamin D levels had less bone loss at the femoral neck compared to patients whose vitamin D level had declined [71]. Furthermore, patients who were randomized to take a high dose of this vitamin presented less hip bone loss than those who received 800 IU daily [72]. This data supports the hypothesis that maintaining normal vitamin D levels is essential to preserve hip bone after surgery. Another study reported that, despite achieving vitamin D serum levels˃30 ng/ml and a calcium intake of 1200 mg/daily, fractional calcium absorption decreased from 33 ± 14 % before BS to 7 ± 4 % in patients after RYGB, leading to a reduction of the absolute amount of calcium absorbed daily (from 392 ± 168 mg to 82 ± 45 mg) [73]. In addition, recent

table 2 Effects of various players on bone and its variation in obese states and after bariatric surgery.

Parameter	Overall action on bone	Variation of the plasmatic level		
		Obese vs. lean state	After surgery	
			SG	RYGB
Leptin	It is likely that leptin has an overall positive effect on bone. The bone effects of leptin can be different, according to the area of the skeleton studied [152].	↑[153]	↓[154]	↓[154]
Adiponectin	Has a dual action with opposite outcomes on bone metabolism, which makes its global effect uncertain [155].	↓[153]	↑[156]	↑[156]
Ghrelin	Clinical data presents variable results, with some studies finding a positive association between ghrelin and BMD [109], while others present no significant association [96, 110] or even a deleterious effect on bone [111].	**= /**↓[122]	↓[122]	↓[122]**/ may be** ↑ **in the long term**[108]
Resistin/Visfatin	Insufficient data to draw any clear role of these hormones on bone.	↑[153]**/ =** [157]	**?**	**?**
Vitamin C	Positive correlation with BMD in multiple bone sites and an association with decreased risk of BMD-independent fractures [76, 77].	↓[158]	**?**	**?**
Vitamin E	Insufficient data. Seems to favor a net increase in bone mass and to promote structural integrity of the skeleton [81].	**?**	**?**	**?**
Vitamin D	Overall positive effects on bone. Prolonged and severe vitamin D deficiency leads to rickets in children and osteomalacia in adults [159].	↓[160]	↑[161] **(but depends on the efficacy of the supplementation)**	↑[161] **(but depends on the efficacy of the supplementation)**
Irisin	Overall positive effects in bone considering the available evidence: low levels correlated with vertebral fractures; higher levels associated with increased BMD/bone strength [128].	↑[162–163]	**?**	**?**
Bile acids	Insufficient data. Positively correlated with BMD and negatively correlated with bone turnover biomarkers reflecting bone absorption in postmenopausal women [140].	↑[164]	↑[139]	↑[139]
FGF-21	Insufficient data, with conflicting results. Some articles show adverse effects on bone while one article on humans states that FGF21 can increase bone mass in women through paracrine mechanisms in the bone–adipose interface [165].	↑[166]	↑**/ =** [146]	↑**(post-prandrial)** [167] **/**↓[166]
GLP-1	Directly affects bone cells and regulates bone turnover by increasing formation and decreasing resorption [115].	↓[168]	↑[107, 169]	↑**post-prandrial = fasting** [170]
GLP-2	Inhibits bone resorption with only minimal effects on bone formation. Four months of treatment with GLP-2 increased hip BMD in post-menopausal women [115].	↓[171]	↑[112]	↑[112]
GIP	GIP has a direct effect on regulation on bone metabolism with anabolic effects on osteoblasts and anti-resorptive effects on osteoclasts [115].	**=**[122]	**= (fasting)** [107] ↑**(post-prandrial)** [122]	**?**[172]
PYY	PYY can play a role in bone mass regulation as evident from association studies in populations with altered energy balance (supported mostly from rodent studies) [115].	↓ [122]	**=** /↑ fasting [122] ↑**postprandrial** [107]	**=** /↑ fasting ↑ postprandial [122]

= : Stable levels; ↑: Increased levels; ↓: Decreased levels; ?: Findings need clarification; Note that this data is based upon several papers, but many areas are still controversial, and studies have had conflicting results. For that reason, the associations may change in the future depending on the new findings in the area. This table aims to present a summary of the most consistent patterns.

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research in pre-menopausal women showed that calcium absorption was impaired after surgery – not only among those submitted to RYGB, but also in those patients undergoing SG (when calcium absorption was significantly reduced from 36.5 ± 2.0 % before SG, to 21.0 ± 2.3 % and 18.8 ± 3.4 % at 12 and 24 months after SG) [74]. This calcium malabsorption is believed to be one on the main reasons for the increased levels of parathormone (PTH) after bariatric surgery that has been described in several studies [16, 37, 71]. Interestingly, some data report that the overall PTH action on bone metabolism could change according to the type of bone (cancellous vs cortical). One study reported that in patients with post-operative increases in PTH levels, lumbar spine BMD remained stable. In addition, other studies where PTH was stable or decreased, showed that BMD decreased, which supports the hypothesis that PTH can have a protective effect on the cancellous bone of the lumbar spine. On the other hand, augmented PTH levels appear to be associated with increased cortical bone loss in the tibia [70, 75]. The true impact of secondary hyperparathyroidism after bariatric surgery on bone metabolism is still a matter of debate nowadays and more studies are needed to clarify this intricate relationship [67]. Another nutritional factor, which could also play a role in bone metabolism after bariatric surgery is vitamin C. It is well known that scurvy (the lack of vitamin C) is characterized by lower values of BMD and bone mineral content. Most research on the impact of vitamin C on bone health in humans has reported a positive correlation with BMD in multiple bone sites and also an association with decreased risk of BMD-independent fractures. The effects of vitamin C include the stimulation of osteoblast maturation and the inhibition of osteoclast activity [76, 77]. Two of the studies carried out on levels of Vitamin C in bariatric patients showed an increased level of this vitamin after RYGB (one and five years after surgery) [78, 79], while another study demonstrated that there was a significant reduction in serum vitamin C levels 24 months after RYGB [80]. The role of this vitamin in bone metabolism after bariatric surgery still needs clarification, as few papers have been published on this issue, and those that have present conflicting results.

Vitamin E – a lipophilic vitamin with antioxidant properties, seems to favor a net increase in bone mass and ensure structural integrity of the skeleton [81]. A review by Lewis et al. found no significant changes to the prevalence of Vitamin E deficiency at 12 months, compared to baseline. Despite this fact, one of the papers included in their review presented a statistically significant decrease in average serum vitamin E levels at six months after BS, and two other papers found a statistically significant decrease in average vitamin E plasmatic levels at 12 months (both compared to baseline) [82]. A more recent systematic review showed that patients undergoing malabsorptive procedures (such as RYGB) are at higher risk of developing vitamin E deficiency, although clinical manifestations of this deficiency are rarely reported [83]. Considering the apparent lower levels of Vitamin E after BS and its bone protective effects, one can hypothesize that this vitamin is another link between BS and its prejudicial effects on bones.

Dietary protein ingestion among bariatric patients after BS tends to be inadequate, which can potentially lead to a decrease in lean body mass, diminished metabolic rates, and physiological damage [84]. A study carried out on a population of 30 women submitted to RYGB revealed that most amino acids increased as early as three months after surgery, which probably reflects muscle catabolism [85]. Recent evidence from a study of 184 patients undergoing SG showed that the proportion of patients with sarcopenia increased one year after surgery (8 % before surgery vs 32 % one year after) [86]. Considering that sarcopenia (reduced muscle mass) is associated with a decrease in BMD and with osteoporosis among human subjects [87, 88], it becomes clear that muscle-bone unit can also play a role in bone metabolism after BS. In addition, other papers have shown that adequate protein intake after BS minimizes muscle and bone loss [32, 89] and raises awareness for the need for a personalized nutritional plan, which can ultimately protect the skeleton of these individuals after surgery, considering patients' metabolic needs.

Hormonal factors

Despite the important role of mechanical and nutritional factors, hormonal changes resulting from anatomical alterations and weight loss also have an impact on bone metabolism after BS. One of the involved hormones is leptin – an adipokine which is released in amounts that are proportional to whole body adipose tissue [90]. Previous data demonstrated that leptin promotes osteoblastogenesis and inhibits osteoclastogenesis through various central and peripheral pathways, and that it also favoring osteoblast differentiation and matrix mineralization [91, 92]. In addition, a decrease in this adipokine after RYGB was inversely correlated with increased levels of markers of bone formation and resorption. The raise of resorption markers was more evident, which indicates an overall effect toward bone loss [93]. This suggests that leptin has a net positive impact on BMD that is then lost – at least partially – as its levels decline after surgery (which is not only observed after RYBG, but also after SG) [94]. Interestingly, impaired leptin signaling in the hypothalamus was found to be a predictor of decreased cortical bone mass and overall BMD or content, albeit with a presumably related increase in trabecular bone formation [95]. Apart from the overall positive effect (supported by a meta-analysis by Biver et al. [96]), there is also evidence that leptin can have a negative impact on bone, due to a central effect through a sympathetic pathway, however further research on this issue is required [92].

Another potential link between BS and bone health is adiponectin – a bone marrow fat-derived hormone which, similar to leptin, does not have a clearly understood role in this relationship. Its serum levels – which are negatively correlated with adipose mass – increase after BS [97]. Circulating adiponectin has been associated with an overall anti-osteogenic effect on bone cells through indirect stimulation of osteoclast formation [98]. Other possible mechanisms that result in bony deleterious effects originate from adiponectin's ability to bind growth factors and decrease plasmatic insulin concentrations, which ultimately counteract the anabolic effects of these hormones on the skeleton [21]. A meta-analysis of 59 papers demonstrated that adiponectin was negatively associated with BMD, independent of peripheral fat mass parameters, menopausal status, and gender [96]. This association was also supported by a prospective study of 42 women 12 months after RYGB [99]. Despite these findings, a correlation between the change in adiponectin and increased plasmatic markers of

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bone turnover was not found in another study of 20 patients who had been submitted to RYGB [93].

The effects of the other two adipokines – visfatin and resistin – in this context are largely unknown. In the case of visfatin, no association between BMD and its circulating levels has been found in the metadata or in other cohort-independent studies [100]. Previous data in non-bariatric patients revealed that resistin was a significant determinant of lumbar spine BMD among middle-aged men [101], and that high serum resistin levels were found to be independent contributors to low BMD in postmenopausal women [102]. Further research is required to clarify whether these adipokines play a role in bone metabolism after BS. Another possible connection between BS and bone loss is estrogen – a sex hormone that can be produced in adipose tissue due to the conversion of testosterone into estradiol under the control of the aromatase enzyme. This is the main process of estrogen generation in both men and postmenopausal women. After BS, levels of estradiol were diminished in both men and women with the expected weight loss and adipose tissue reduction [103]. Considering that estrogen acts to promote bone formation and suppress bone absorption [104, 105], the reduction of its levels after BS could be another explanation for metabolic bone changes after surgery.

In turn, the role of ghrelin in BS is still not very clear. This hormone – which is produced in the gastric antrum and fundus – is thought to be an important player in the long-term maintenance of energy stores as it stimulates appetite and decreases energy expenditure [106]. A meta-analysis of 28 studies by McCarty et al. revealed that fasting serum ghrelin levels decreased after SG [107], while another by Xu et al. of 16 papers showed that levels of ghrelin decreased in the short term ($\leq$ 3 months), and increased in the long term (> 3 months) after RYGB [108]. While studies in animals suggest an overall anabolic effect of this hormone on bone, clinical data presents variable results, with some studies finding a positive association between ghrelin and BMD [109], while others present no significant association [96, 110], or even a damaging effect on bone [111]. Accordingly, the impact of ghrelin on bone after BS remains still remains to be determined [21]. The glucagon-like peptides GLP-1 and GLP-2 – which are produced by intestinal L cells in response to food intake – are two hormones whose postprandial circulating levels are increased after RYGB and SG [112, 113]. Similar to teduglutide, GLP2 receptor agonists are used in the treatment of short bowel disorders, as they increase both the bowel surface area and absorption [114]. The few papers to date on the effects of GLP-2 on human bone in vivo have showed that GLP-2 inhibits bone resorption (measured as CTX), with only slight effects on bone formation (measured as P1NP or osteocalcin). Research carried out on post-menopausal women found conflicting results, with one study demonstrating that four months of GLP-2 treatment increased hip BMD [115], while another found no association between GLP-2 activity and osteoporosis [116]. In turn, studies in humans concluded that GLP-1 has benefic effects on bone metabolism, probably through augmented bone formation. No effect on serum CTX concentration was seen [117]. One of these investigations was conducted in weight reduced women with obesity (after diet induced weight loss) and found that treatment with a long-acting GLP-1 receptor agonist increased bone formation by 16 % and prevented bone loss after weight loss following a low-calorie diet [118]. This fact gains even more relevance when we consider that GLP-1 receptor agonists are therapeutic options not only before but also after bariatric surgery [119]. Studies in rats also support the positive impact of GLP-1 on bone strength and quality, which sheds some light on the presumed role of this incretin in protection against bone loss [115, 117]. Despite these facts, recent evidence from the meta-analysis shows that treatment with GLP-1 receptor agonists does not alter the risk of bone fracture, when compared with treatment with other antidiabetic drugs among patients with type 2 diabetes [120].

The gastric inhibitory peptide (GIP) – which is produced by the k-cells in the proximal small intestine after food ingestion – is a hormone with apparently positive effects on bone [67]. Evidence from studies in humans show that GIP reduces CTX independently of insulin, and that a loss-of-function of GIP receptor is associated with decreased BMD, together with an increased risk of fracture. Studies in vitro found that GIP also inhibits osteoclast formation and resorption, while it reduces osteoblast cell death [115]. One interesting article from Torekov et al. also found an association between a functional GIP receptor polymorphism Glu354Gln (rs1800437) and BMD and fracture risk, suggesting the involvement of GIP in the regulation of bone mineral density [121]. Considering several studies have found that the fasting and postprandial levels of this hormone decreased after RYGB, GIP could be another connection in the complex influence of BS on bone. Interestingly, GIP levels after SG were stable, or even increased – which raises several unanswered questions about this issue [122].

Another gut hormone is Peptide YY (PYY) – a regulator of food intake that is secreted by the enteroendocrine L cells of the distal gastrointestinal tract. It is known that postprandial PYY levels are increased after RYGB and SG, although it remains unclear whether the same happens during fasting [21, 122]. Studies of the impact of GIP on bone in humans found an inverse relationship between plasmatic GIP and BMD in populations with weight loss (↑PYY and ↓BMD among patients with anorexia nervosa or submitted to RYGB). There is also evidence for the direct effect of PYY on osteoblast and osteoclast activity, with a negative association between PYY and osteoclast activity. In addition, mice without PYY receptors presented an increase in bone mass and strength, although more research is required to clarify the existent controversies regarding the effects of PYY on bone [115].

Acknowledged factors for future lines of research

During the last decade, the impact of microbiota in multiple aspects of metabolic health of the human host has been established with ample evidence [123]. It is known that microbiota are profoundly affected by BS, with an increase of Bacteroides and Proteobacteria, and a decrease in Firmicutes post-operatively in most studies [124]. It is only now that the first steps are being taken to study the influence of microbiota on bone and its related diseases [125, 126]. Interestingly, it is known that several members of the Proteobacteria (augmented after BS) are associated with osteoporosis [125]. Despite this fact, the only paper that to our knowledge exits which addresses the relationship between microbiota and BMD found that gut microbiota presents little relevance for BMD

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[127]. Considering the lack of information regarding the impact of changes microbiota after BS on bone, it is still too early to state whether gut bacteria have a clear role in this issue.

During the past few years, the relation between irisin and bone has been often in the spotlight [128–130]. Irisin is a molecule that is produced and released by myocytes, which appears to have an overall positive effect in bone metabolism. The available evidence shows that low levels of irisin are associated with vertebral fragility fractures among post-menopausal women, and that levels of irisin are correlated positively with BMD among geriatric men [128, 131]. It is also known that this molecule is associated positively with BMD and bone strength in athletes, and research carried out on children described a positive association between serum irisin and bone status in healthy children [128]. These benefic effects could be explained, at least in part, by the stimulating effect of irisin on osteoblast proliferation and differentiation [132]. Intriguingly, evidence also exists that treatment with irisin increases sclerostin production by osteocytes (leading to bone resorption) and that the deletion of FNDC5 (precursor of irisin) prevents ovariectomy-induced trabecular bone loss [133]. Another article which supports these findings concluded that irisin directly stimulates both osteoclastogenesis and bone resorption in vivo and in vitro [134]. With regards the levels of irisin after SG, it was found that irisin levels increased after six months [135], while another study found no change in its levels after surgery [136]. A third study stated that circulating irisin levels decreased after SG and RYGB in comparison to the baseline [137]. Similar to SG, post-RYGB irisin levels also present conflicting results in several papers [67]. Accordingly, the impact of irisin on bone still needs enlightenment, and this issue represents a promising area of research among bariatric patients.

Bile acids (BA) are another player that has gained increasing attention over the decade of 2010 to 2020 [138]. Accumulating evidence has shown that levels of total fasting and postprandial plasma BA increase after SG and RYGB and it is thought that these changes contribute to improved lipid and glucose homeostasis, insulin sensitivity, and energy expenditure after BS [139]. BA also seem to have a metabolic effect on bone, with a study in postmenopausal women revealing that total serum BA was positively correlated with BMD, and negatively correlated with bone turnover biomarkers of bone resorption [140]. In addition, studies in mice found that the activation of the FXR BA receptor significantly promoted osteoblastic differentiation and that FXR agonists suppressed osteoclast differentiation from bone marrow macrophages. A histological study of mice lumbar spine also demonstrated that FXR deficiency impaired bone formation rate, as well as trabecular bone volume and thickness [141]. Interestingly, different types of BA can have differing effects on bone. Ursodeoxycholic acid inhibits apoptosis and increases survival and differentiation of human osteoblasts, thus neutralizing the detrimental effects of lithocholic acid in these processes [142]. The effects of BA on bone among patients submitted to BS are still not known, and this could be another interesting line of future research.

FGF-21 is a hormone that is produced in the liver and adipocytes, which is positively associated with poor metabolic health, being related with obesity, diabetes, mitochondrial diseases, and ageing. It is also known that FGF-21 has several musculoskeletal effects and that it is involved in muscle atrophy, bone loss and reduced BMD [143]. One of the few studies addressing FGF-21 levels after BS showed a significant increase in fasting FGF21, especially one month after surgery [144], while other stated that there was a 63% reduction in FGF-21 levels six months after SG [145]. A paper from Khan et al. reported that fasting and 120-minute postprandial FGF21 levels at one month were increased, although these levels returned to baseline values three months after SG [146]. In turn, Gómez-Ambrosi et al. found that FGF21 levels were reduced one year after SG-induced weight loss, but not after RYGB [147]. Therefore, the limited evidence regarding FGF-21 and its impact on bone after BS presents new opportunities for research in bariatric patients.

Other possible interesting line of research is the effect of diet-induced weight loss effects on bone mass. A recent systematic review and meta-analysis of clinical trials found that, in patients with overweight and obesity not submitted to bariatric surgery, a single diet-induced weight-loss intervention leads to a small decrease in total hip BMD (with decreases of 0.010 to 0.015 g/cm^2), but not in lumbar spine BMD (in which was not observed any statistically significant effect of diet-induced weight loss, the same happening with whole body BMD) [148]. A subsequent paper, addressing this issue among older adults with obesity, stated that several prospective observational and interventional studies confirm the negative effects on skeletal health outcomes of intentional weight loss achieved by lifestyle changes. These effects seem to be modest but persistent in the long term [149]. So, it would be interesting to know if different long-term dietary patterns after bariatric surgery can modulate bone metabolism and these effects on bone mass.

Bariatric surgery is also an option for several patients with heterozygous mutations of genes related with genetic obesity (such as MC4R, POMC, PCSK1, SIM1, or PTEN) [150]. Patients with mutations in MC4R gene had higher BMD than matched control participants, underlining a probable influence of genes in these relationship between obesity and bone metabolism (that can, in theory, be also a factor to consider after bariatric surgery) [151].

Conclusion

The impact of bariatric surgery on bone is field of research that has seen a significant breakthrough over the last decade of 2010 to 2020. Several factors that have an impact of bariatric surgery on bone health have been identified, however, how they interact to regulate bone metabolism after metabolic surgery is still largely unknown. For this reason, we believe that this area of research will progress positively and advances the frontier of knowledge over the next decade. Understanding these relationships is crucial to avoid bone loss and to decrease fracture risk after BS and raises awareness of this problem and can possibly lead to improving therapeutical options.

Conflict of Interest

The authors declare that they have no conflict of interest.

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In addition to the presented effects in bone metabolism, BS also induces significant changes in body composition[1], a concept referring to the proportions of different body tissue components that make up a person´s body[2] (as depicted in Figure 1). These changes, that encompass both reductions in fat and lean body mass, are documented as early as one month after the procedure, but remain to be clarified[3].

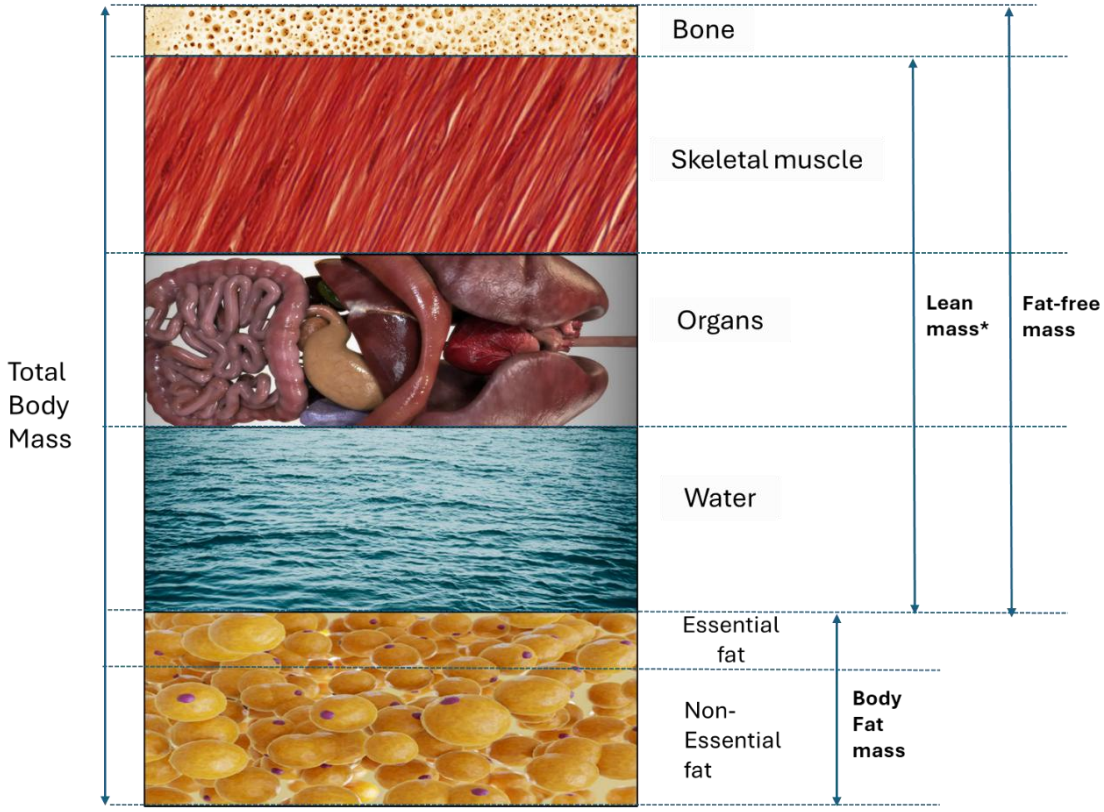


Figure 1 Body composition components according to the definitions used by Dual X-Ray Absorptiometry (DEXA). The proportion of each component varies depending on the evaluated individual[4-6]. *Some sources also include essential fat as part of the lean mass[4].

Different methods are used to evaluate body composition, including anthropometric measurements, bioimpedance, Dual X-Ray Absorptiometry (DEXA), magnetic resonance imaging (MRI), computed tomography (CT), ultrasonography (US), among others (reviewed in more detail elsewhere)[7-9]. Despite the high accuracy of MRI and CT (which provide quantitative and qualitative assessments of muscle mass,

subcutaneous and visceral fat), these methods are expensive, presenting poor accessibility, and high radiation doses (in the case of CT)[10]. US has emerged as an increasingly important tool for body composition assessment in clinical settings, offering an accessible, cost-effective with no radiation, and portable alternative to other methods [11]. Despite its growing relevance (particularly in studying skeletal muscle), US presents some limitations, including its dependency on the examiner, which can introduce evaluation errors and reproducibility issues. In addition, the wide range of commercially available US devices showing great technological and calibration differences (even greater than those observed with DEXA), hampers the comparison of different studies[12]. Bioelectrical impedance analysis (BIA) is one of the most used tools to evaluate body composition of bariatric patients in the clinical practice[8]. BIA provides estimates of body fat, free-fat mass and water distribution through the application of a low-amplitude electrical current across the body. It offers several advantages such as its simplicity, portability and inexpensiveness (mainly with single-frequency BIA devices), conveniency and reproducibility[8, 13]. Multifrequency BIA appears to be a reliable technique among individuals with obesity, demonstrating an excellent correlation with DEXA in the assessment of fat and fat-free mass in patients with class II/III obesity[14]. Despite its positive points, BIA can be prone to measurement errors depending on exercise status, hydration levels, body temperature, alcohol consumption or even food intake[4, 12].

Among all body composition assessment methods, DEXA has been considered the most suitable for clinical research, being also an important tool in clinical practice[8]. In this method, X-rays at two different energy levels are applied to distinguish bone (by measuring bone mineral content) from soft tissue, including lean mass and fat mass proportions. Unlike CT, DEXA is less expensive, and the amount of radiation used is minimal, being much smaller than a chest X-ray[4, 15]. It is also considered a fast method (10 – 20 minutes), more accessible that MRI and CT, while presenting high accuracy in this context[8]. Thus, DEXA can be applied to track changes in lean and fat tissues

among individuals with obesity undergoing substantial weight loss, such as following BS, in accordance with an official position of the International Society for Clinical Densitometry. Serial DEXA evaluations may help to identify bariatric patients who are losing excessive amounts of lean mass (which may be more pronounced after hypoabsorptive techniques such as Roux-en-Y gastric bypass), thereby allowing for additional nutritional and exercise interventions to prevent muscle loss[16]. Despite the advantages of DEXA, this method is limited by table weight and size constraints (which may prevent the evaluation of heavier patients) and can also be affected by motion artifacts. In addition, DEXA is less precise in measuring the tissues of the trunk area compared to the limbs and has a lower resolution compared with CT and MRI[8, 9, 16].

Body composition has received increasing attention over the past decades, given its importance in several processes such as the assessment of nutritional status and its changes, the impact of physical activity, the monitoring of therapeutic interventions, among others[17, 18]. In addition, evaluating the proportion of each body component can also predict general health and all-cause mortality. A meta-analysis of prospective studies found that each 5 kg increase in fat mass was associated with a 6% higher risk of death (95% CI 1.01-1.12; 10 studies) while each 10% increase in body fat percentage was linked to a mortality hazard ratio of 1.11 (95% CI 1.06-1.16; 7 studies)[19]. Interestingly, increased fat mass proportion can be seen in various body mass index categories, being related to an increased risk of cardiometabolic diseases even among adults with normal weight[20]. On the other hand, low lean mass (often used as a surrogate for skeletal muscle mass, its main component) was linked with an increment of 30% in the all-cause mortality risk among the middle-aged and older population in another recent meta-analysis including more than 130 000 participants[21]. This can partially explain why underweight patients present increased all-cause mortality despite presenting low fat mass [22]. Skeletal muscle is an organ that was initially associated with mechanical function, but nowadays it is known that muscle interferes with several other functions of our body such as the neurological, metabolic and endocrine, having

also a seemingly important role in mood regulation [23, 24]. This influence is achieved through the action of myokines, which are cytokines and other peptides, that are produced and released by muscle fibers. These myokines (that encompass interleukin-6, myostatin, irisin, among many others) exert autocrine and paracrine effects within muscle cells. In addition, they can also act in distant organs, by having a role in the "browning" of white adipose tissue, bone formation regulation, inflammation, glucose homeostasis and insulin secretion, lipolysis, endothelial function, among many others[12, 24]. Therefore, it is not surprising that muscle mass preservation became one of the main priorities after BS[25]. Interestingly, obesity itself can contribute to the loss of muscle mass and function through adipose tissue related disturbances, including oxidative stress, insulin resistance and inflammation, all of which impair muscle health[26, 27]. The simultaneous presence of excess fat mass (in the context of obesity) and loss of muscle mass and function (sarcopenia) is referred to as sarcopenic obesity (SO). This condition, more precisely defined in a recent Consensus Statement by European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO), carries an increased risk of occurrence in bariatric patients, both before and after BS [28, 29]. After surgery, the intolerance to protein food sources (such as red meat), poor adherence to protein supplementation and disordered eating behaviors, sedentarism, aging and inflammatory comorbidities, can contribute to diminished muscle mass and SO. This can be also followed by a possibility of weight regain, composed mainly of adipose tissue, increasing the risk of excessive fat mass[29]. Although SO has gained relevance over the past decade, data remain limited, a situation further complicated by the different diagnostic criteria applied[30]. This explains why SO prevalence in the context of BS is highly heterogeneous, requiring further clarification [29], which we intend to address in this thesis.

CHAPTER 2

PURPOSE

PURPOSE

This thesis aimed to clarify the impact of bariatric surgery on bone metabolism and body composition. By understanding this, we can potentially pave the way for better follow-up care after surgery regarding vitamin/mineral supplementation, nutritional approach and physical exercise.

The main objectives were the following:

1. To compare the impact of Roux-en-Y gastric bypass and Sleeve gastrectomy in the bone mineral density of the lumbar spine, total femur, femoral neck and whole body, one and two years after surgery.

2. To compare these two bariatric techniques regarding their impact in body composition assessed by Dual-Energy X-ray Absorptiometry, focusing on changes in bone mineral content, lean mass and fat mass one and two years after surgery.
   (objectives 1. and 2. are addressed in article 1)

Other specific objectives were the following:

3. To clarify the differences between these two procedures regarding the variation of parameters of bone metabolism and fracture risk (calculated by FRAX®)
   (addressed in article 1)

4. To study the prevalence of secondary hyperparathyroidism (SHPT) before, 1 and 4 years after bariatric surgery, considering the type of surgery performed.

5. To clarify the differences between bariatric patients with and without SHPT.

6. To find predictors of SHPT 1 year and 4 years after bariatric surgery.

(objectives 4-6 are addressed in article 2)

7. To assess the effects of bariatric surgery on different degrees of sarcopenic obesity severity (by comparing variations on body composition, bone metabolism markers, cardiometabolic parameters and remission of comorbidities) (addressed in article 3).

8. To clarify the impact of menopause status at the time of surgery and changes in bone mineral density, body composition and cardiometabolic risk factors after surgery (addressed in article 4).

9. To explore whether the endocrine pathways involving FGF-21 and FGF-23 may help explain bone mineral density changes after bariatric surgery, by assessing the association between their circulating levels and BMD variation over two years, and comparing their variation after sleeve gastrectomy and Roux-en-Y gastric bypass (addressed in article 1- cont.).

CHAPTER 3

RESULTS

The results of this thesis will be addressed in the form of published articles. The first article will be followed by a supplementary subsection (not published) examining the influence of FGF-23 and FGF-21 levels in bone mineral density after surgery. The methodology and discussion of each individual paper is also presented in the publication. A global discussion encompassing all the main aspects of this project is shown in Chapter 4.

The articles are the following:

1. Mendonça F, Soares P, Leite AR, Maia M, Neves JS, Luís C, Rodrigues I, Carvalho L, Alves J, Fonseca B, Pinto BS, Silva B, Barbosa J, Couto L, Moreno T, Canha M, Pedro J, Festas D, Varela A, Oliveira A, Faria T, Fernandes A, Vieira A, Ndrio A, Guimarães JT, Lima-Da-Costa E, CRIO, Soares R, Freitas P. Bone Metabolism And Body Composition 24 Months After Sleeve Gastrectomy And Roux-en-Y Gastric Bypass – The Bariatric Bone Study. Obes Surg. 2026 Apr; 36: 2901–2913.

   1.cont. Mendonça F, Soares P, Leite AR, Maia M, Neves JS, Luís C, Rodrigues I, Carvalho L, Alves J, Fonseca B, Pinto BS, Silva B, Barbosa J, Couto L, Moreno T, Canha M, Pedro J, Festas D, Varela A, Oliveira A, Faria T, Fernandes A, Vieira A, Ndrio A, Guimarães JT, Lima-Da-Costa E, CRIO, Soares R, Freitas P. Evaluating the Roles of FGF-21 and FGF-23 in Bone Metabolism After Bariatric Surgery: Reminiscences from the BARIATRIC BONE Study (data not published)

2. Mendonça FM, Neves JS, Silva MM, Borges-Canha M, Costa C, Cabral PM, Guerreiro V, Lourenço R, Meira P, Ferreira MJ, Salazar D, Pedro J, Viana S, Souto S, Varela A, Belo S, Lau E, Freitas P, Carvalho D; CRIO group. Secondary Hyperparathyroidism Among Bariatric Patients: Unraveling the Prevalence of an Overlooked Foe. Obes Surg. 2021 Aug;31(8):3768-3775.

3. Rodrigues PS* & Mendonça FM*, Neves JS, Luís C, Rodrigues I, Moreno T, Festas D, Pedro J, Varela A, Fernandes A, Costa EL; CRIO group; Freitas P. Effects of Bariatric Surgery on Sarcopenic Obesity Outcomes: A One-Year Prospective Study in Middle-Aged Women. Obes Surg. 2024 May;34(5):1674-1683.

4. Maia M* & Mendonça F*, Leite AR, Soares P, Neves JS, Luís C, Rodrigues I, Moreno T, Pedro J, Festas D, Varela A, Oliveira A, Faria T, Fernandes A, Vieira

A, Ndrio A, Guimarães JT, Costa EL, CRIO, Soares R, Freitas P. Impact of Menopausal Status on Bone Metabolism and Body Composition After Metabolic-Bariatric Surgery: a Two-Year Prospective Study in Middle-Aged Women. Obes Surg. 2026 Apr;36(4):1705-1717.

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Article 1

Bone metabolism and body composition 24 months after sleeve gastrectomy and Roux-en-Y gastric bypass among women – The BARIATRIC BONE study

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Obesity Surgery

Published in 2026.

Obesity Surgery (2026) 36:2901–2913
https://doi.org/10.1007/s11695-026-08672-8

RESEARCH

Bone Metabolism And Body Composition 24 Months After Sleeve Gastrectomy And Roux-en-Y Gastric Bypass – The Bariatric Bone Study

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Received: 20 November 2025 / Revised: 6 February 2026 / Accepted: 7 March 2026 / Published online: 18 April 2026
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Abstract

Introduction Despite the benefic impact on weight management and obesity-related comorbidities, bariatric surgery (BS) presents deleterious effects on bone health. The differential outcomes of the two main bariatric techniques on bone metabolism and body composition still need to be clarified.

Methods Prospective single-centre study of female participants who underwent BS between November/2019 and December/2022, followed for at least 12 months. We compared the impact of Roux-and-Y gastric bypass (RYGB) and Sleeve gastrectomy (SG) on the variation of bone mineral density (BMD), body composition and bone metabolism markers [such as osteocalcin and beta-crosslaps (CTX)] after BS. Linear regression was used to evaluate predictors of T score reduction after BS.

Results Of the 162 included patients, 99 (61.1%) underwent RYGB and 63 (38.9%) SG. Total femur BMD significantly decreased one and two years after BS, with a steeper reduction in the RYGB group. Two years after surgery, RYGB led to a greater BMD decline in femoral neck (-0.09 ± 0.07 vs. -0.12 ± 0.07 g/cm^2, $p = 0.049$). RYGB group also presented more fat loss at both time points, with no differences in lean mass reduction at one (-6.3 ± 3.4 vs. -6.3 ± 2.9 kg, $p = 0.38$) and two years (-7.4 ± 3.4 vs. -7.4 ± 3.0 kg, $p = 0.11$). Osteocalcin and CTX increased at both time points, with a significantly higher increase in RYGB group. RYGB was predictor of BMD reductions in all these three areas, even after adjusting for age.

Conclusions RYGB showed a greater impact in bone metabolism and body composition than SG, with noticeable effects in the hip bone and fat mass reduction.

Key points

- Bariatric surgery presents deleterious effects on bone health.
- RYGB induced greater bone mineral density loss at the hip.
- RYGB led to greater fat mass loss with no differences in lean mass loss.
- Almost half of patients presented osteopenia or osteoporosis 2 years after surgery.

Keywords Bariatric surgery · Bone metabolism · Body composition · Bone mineral density · Osteocalcin · CTX

Introduction

Obesity is a chronic disease that has become a prominent global health issue [1]. According to estimates from the World Obesity Federation, in 2024 more than one billion people were affected globally by this disease. It also predicted that most of the global population (51%) will fulfill the criteria for overweight or obesity by 2035 [2, 3]. Considering these numbers, it is not surprising that bariatric surgery (BS) represents nowadays a widely used therapeutic

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option for patients with severe obesity, presenting substantial improvements not only in weight but also in several associated conditions such as diabetes mellitus, hypertension, dyslipidemia, sarcopenic obesity, among many others [4, 5]. Despite these undisputed benefits, the putative negative impact of rapid weight loss in bone metabolism has become a hot topic mainly during the last decade [6]. Bone deterioration occurring after bariatric surgery results from multiple players such as reduced calcium and vitamin D absorption (with associated secondary hyperparathyroidism), mechanical unloading and changes in adipocyte and gastrointestinal hormone levels [7, 8]. Despite the increasing body of evidence to support the deleterious effects on bones of both sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB), the number of prospective studies directly comparing these techniques are scarce, and have a limited number of patients (usually less than 70) during a follow-up period of one year in most cases [9, 10].

Therefore, the main objectives of this study are to compare the impact of RYGB and SG in body composition and bone mineral density, also including the evaluation of parameters of bone metabolism and fracture risk (calculated with FRAX) during the two years following surgery.

Methods

Subjects and study design

This prospective single-center study included female participants who underwent bariatric surgery (BS) in our tertiary hospital. These patients were consecutively selected from November/2019 to December/2022 during pre-operative assessments of the Integrated Responsibility Center for Obesity (CRIO).

The eligibility criteria included: (a)women aged 40–65 years (b)meeting the criteria for BS - Body Mass Index (BMI) ≥ 35 kg/m² with at least one associated comorbidity or BMI ≥ 40 kg/m² despite their comorbidities; (c)at least one year of non-surgical approaches to obesity without satisfactory weight loss; (d)obesity not related to endocrine diseases; (f)submitted to SG or RYGB; (e)follow-up for at least one year after BS, including Dual-Energy X-ray Absorptiometry (DXA) evaluation before and at 12 and/or 24 months after surgery.

The exclusion criteria encompassed: (a)second or revisional BS; (b)weight exceeding 140 kg (due to technical issues); (c)non-stabilized psychiatric conditions or narcotic/alcohol dependence; (d)previous (during the year before recruitment) or current systemic therapy with corticosteroids or with estrogens as hormonal replacement therapy; (e)thyrotoxicosis; (f)concomitant malabsorption (e.g. celiac disease, previous intestinal disease, short bowel syndrome); (h)severe disease, including cardiovascular, pulmonary, renal, hepatic, osteoarticular, and malignant neoplasms; (i) previous or current anti-osteoporosis therapy; (j)therapy with thiazolidinediones, canagliflozin or valproate; (k)hypercalcemia (defined by an albumin-corrected calcium>10,2 mg/dL) or glomerular filtration rate ≤ 30mL/min/1,73m^2; (l)diseases affecting bone metabolism (primary hyperparathyroidism, Paget disease of bone, osteoporosis).

Of the initial 200 eligible patients, 17 did not undergo surgery, 1 died and 3 initiated systemic corticoid therapy shortly after enrollment; one patient had osteoporosis, another had hyperparathyroidism, with a case of hypoparathyroidism and a prolactinoma being detected at baseline. Three patients presented hyperthyroidism and other two were diagnosed with metastatic malignant tumors before surgery. Five patients were lost to follow-up shortly after surgery, and three did not collect data regarding baseline densitometric parameters. Thus, 162 patients were included in this study (a flowchart is provided as Supplementary image 1).

The enrolled patients were divided in two groups according to the performed type of surgery technique, that was determined by the surgical team considering the best clinical practice. RYGB was preferred in cases of higher BMI, patients with comorbidities (such as diabetes mellitus, hypertension, dyslipidemia), gastroesophageal reflux, esophagitis or suspected hiatal hernia. In the extremes of age, SG was more commonly chosen. In all cases, patient preference was also considered when selecting the surgical technique. The surgical techniques in our high-volume surgical center were standardized, with RYGB having a biliopancreatic limb of 100 cm and an alimentary limb of 120 cm.

Patients who developed osteoporosis during the study were excluded and treated accordingly.

After the procedure, a hypocaloric diet was prescribed, consisting of 1200 kcal/day for women and 1500 kcal/day for men. Food consistency was adjusted during the postoperative period, with a liquid diet in the first month followed by a soft diet in the second month. All patients were supplemented with multivitamin supplements, with the addition of specific supplements (such as vitamin D and, less commonly, calcium carbonate). Vitamin D supplements were either cholecalciferol oral solution (0.5 mg/ml, 667 international units per droplet), cholecalciferol pills (between 22,400 and 30,000 international units per pill) or calcifediol pills (0.266 mg per pill), prescribed and adjusted according to the degree of vitamin D deficiency presented in the postoperative analysis (at least 3000 IU/day and as high as 6000 IU of cholecalciferol/day, independently of the surgical technique). Calcium carbonate supplements (1500 mg per day) were added according to calcium corrected to albumin levels and in some cases of secondary hyperparathyroidism as an add on to vitamin D supplements.

This study followed the protocol approved by the Ethics committee of our centre. All procedures were executed in accordance with the international recommendations of Good Clinical Practice, the Declaration of Helsinki, and the applicable legislation.

Pre- and post-operative evaluations

The evaluations were carried out prior to surgery, and at 6, 12, and 24-months post-surgery. Body composition was measured using DXA with a properly calibrated densitometer (Lunar iDXA model). The evaluated parameters included total body fat, the proportion of fat mass, trunk fat mass, leg fat mass, arm lean mass, leg lean mass, and bone mineral content (BMC). Additional measurements taken included bone mineral density, T score and Z score at various sites: the lumbar spine (L1–L4), total femur, femoral neck and full body. Osteoporosis was diagnosed with a T score ≤ -2.5 standard deviations (SD) at any measured location [11]. Osteopenia was defined by a T score between − 2.5 SD and − 1.0 SD [12].

Anthropometric data, including body weight (W), height (H), waist circumference, and body mass index (BMI), were recorded. Blood pressure readings were taken during endocrinology appointments, with the patient seated for a minimum of 5 min.

Blood samples were drawn after a fasting period of at least 12 h. The biochemical parameters analyzed in the study encompassed total protein levels, low-density lipoprotein (LDL), iron, transferrin, ferritin, folic acid, vitamin B12, vitamin D, albumin-corrected calcium, phosphorus (P+), magnesium (Mg), parathyroid hormone (PTH), thyroid-stimulating hormone (TSH), hemoglobin A1c (HbA1c), Vitamin C, Vitamin E, total bile acids (TBA) and urinary albumin-to-creatinine ratio (from a casual urine specimen). Bone turnover markers [osteocalcin and s-carboxy-terminal cross-linked telopeptide type 1 collagen (CTX)] were also assessed. The risk of fracture was calculated with FRAX® adjusted for the Portuguese population [13], considering the baseline and the variation of parameters during 12 and 24 months after surgery. The estimated glomerular filtration rate (eGFR) for each participant was calculated using the CKD-EPI equation. Sarcopenic obesity was diagnosed based on the 2022 consensus proposed by ESPEN and EASO, being determined by the sum of the lean mass of arms and legs (appendicular lean mass (ALM)) adjusted to body weight (BW). The diagnosis was established with a proportion of fat mass ≥ 41% and a ALM/BW ratio < 23.47% [14].

Medical history, including details about pre- and post-surgical comorbidities, medications and supplements, as well as menopause status, and lifestyle factors (including smoking and alcohol habits), were obtained from the participants' medical records. The study also assessed the presence of type 2 diabetes mellitus (DM2), hypertension (HT) and dyslipidemia both at baseline and after a 1-year follow-up period. DM2 was diagnosed if the fasting glucose level was ≥ 126 mg/dL, the HbA1c level was ≥ 6.5% or if the patient was using antidiabetic medication. HT was defined by a systolic blood pressure (SBP) ≥ 140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg, with the current use of antihypertensive drugs also serving as a diagnostic criterion. Dyslipidemia was identified when LDL levels were ≥ 130 mg/dL, HDL levels were ≤ 50 mg/dL, triglycerides (TG) were ≥ 150 mg/dL, or total cholesterol (CT) was ≥ 240 mg/dL. Participants taking statins or fibrates were also considered to have dyslipidemia. Remission of any of these conditions was defined as the absence of diagnostic criteria for a comorbidity (previously diagnosed preoperatively) in the evaluations performed 1 or 2 years after BS.

Statistical analysis

Continuous normally distributed variables were presented as mean ± standard deviation and non-normally distributed continuous variables as median (minimum, maximum). Count and percentages were used to present categorical variables. Participants were divided into two groups based on the performed surgical technique. Clinical, analytical and densitometric parameters at baseline, as well as their variations between baseline and 6, 12, and 24 months after surgery, were compared according to surgical technique using t-student tests, for parametric variables, Mann-Whitney U tests, for non-parametric variables, and chi-squared tests, for categorical variables. Linear regression analysis adjusted for age and surgical type was performed to find predictors of BMD variation after surgery. Logistic regression analysis adjusted for age and weight variation was conducted to find predictors of osteopenia or osteoporosis 2 years after surgery. Comparisons of the prevalence of osteopenia and osteoporosis, BMD, and bone turnover markers between baseline and 6-, 12-, and 24-months post-bariatric surgery (BS) were performed using McNemar's test, paired t-tests, or Wilcoxon tests, according to the distribution of the variables.

Baseline predictors of lumbar spine, femoral neck and total femur T-score variation two years after BS were assessed using logistic regression models unadjusted and adjusted for age and type of surgery.

Reported p-values are two-tailed and $p \leq 0.05$ was considered statistically significant. Analyses were conducted with the use of STATA 18.0® software.

Results

Baseline characteristics

The study enrolled a total of 162 female participants, presenting a mean age of 50.8 ± 7.3 years old and a mean BMI of 42.1 ± 4.7 kg/m^2. Most of the patients were submitted to RYGB (99 individuals; 61.1%) and the remaining ones underwent SG (63 individuals; 38.9%). The overall prevalence of osteopenia at baseline was 21%. There were no differences between groups before surgery regarding the evaluated anthropometric parameters and in the prevalence of several comorbidities (Table 1). The densitometric parameters also presented no substantial differences before surgery, except for a slightly higher total femur BMD among patients submitted to RYGB (1.15 ± 0.14 vs. 1.20 ± 0.13 g/cm^2, p = 0.033) (Table 2). The comparative analysis of analytical parameters at baseline revealed no statistically significant differences between groups, except for albumin-corrected calcium that presented slightly higher levels in the SG group (9.44 vs. 9.30 mg/dL, p = 0.007) (Table 3).

Variation of evaluated parameters after surgery

Focusing on anthropometry and body composition, individuals submitted to RYGB presented a greater reduction in weight and BMI one and two years after surgery. This group of participants presented a higher loss of body fat mass during these two evaluations. Despite decreasing in both groups, there was no difference between surgical techniques regarding the reduction of total lean mass one (-6.3 ± 3.4 vs. -6.3 ± 2.9 kg, p = 0.38) and two years after surgery (-7.4 ± 3.4 vs. -7.4 ± 3.0 kg, p = 0.11) (Table 2).

Regarding BMD variations, total femur was the only area already presenting differences one year after surgery, with more pronounced reductions in the RYGB group (-0.09 ± 0.06 vs. -0.13 ± 0.06 g/cm^2, p = 0.003), a finding that was also observed with associated mean T and Z scores. These differences in total femur BMD were also observed two years after surgery (mean reduction from baseline: 14.8% after RYGB and 11.2% after SG) (Fig. 1). There were no differences between groups at femoral neck BMD one year after surgery, but there was a greater BMD decline in this area two years after RYGB (-0.09 ± 0.07 vs. -0.12 ± 0.07 g/cm^2, p = 0.049; mean reduction from baseline: 11.5% after RYGB and 8.8% after SG). Patients that underwent RYGB also showed a greater BMC loss at one (-0.12 ± 0.14 vs. -0.19 ± 0.11 g, p = 0.004) and two years after surgery (-0.20 ± 0.12 vs. -0.31 ± 0.14 g, p < 0.001). There were no differences between groups regarding hip and major FRAX® scores at baseline or after surgery (Table 2).

After BS, seven patients developed bone fractures. Five were classified as fragility fractures (two in the radius, one in the proximal humerus, another in the fibula and one in two ribs). Six of the seven patients were previously submitted to RYGB. Three of these seven patients (two of the fragility fractures and one traumatic) had a diagnosis of osteoporosis during this study and were under antiosteoporotic treatment at the time of the fracture.

Regarding the variation of analytical parameters (Table 3), there were no significant differences between groups after surgery regarding PTH and albumin-corrected calcium levels. Vitamin D levels showed a greater increase after SG one year after surgery (13.1 ± 12.6 vs. 7.8 ± 12.8ng/mL, p = 0.013), with no differences two years after. Osteocalcin and CTX were more markedly augmented after RYBG than SG one and two years after surgery (Supplementary Figs. 2 and 3). This finding was already observed 6 months after RYGB in the case of CTX (Supplementary table A). The 24-hour urinary calcium increased after SG and decreased after RYGB, a finding that occurred in both time periods. The variation of total fasting bile acids one and two years after surgery also showed statistically significant differences between procedures, remaining stable after SG and increasing after RYGB, particularly at two years.

The prevalence of osteoporosis, osteopenia, sarcopenic obesity and remission of associated comorbidities were not different between groups after BS (Supplementary table B). Almost half of all patients presented osteopenia or osteoporosis two years after BS (Fig. 2). There were no significant

Table 1 Baseline characteristics of the overall sample and comparison between surgical techniques

Variable	Overall sample (n=162)	SG (n=63)	RYGB (n=99)	P value
Age$^{\Delta}$	50.8 ± 7.3	51.8 ± 8.1	50.1 ± 6.7	0.13
Weight (kg) $^{\Delta}$	108.2 ± 13.5	107.0 ± 15.6	109.1 ± 11.9	0.34
BMI (kg/m^2) $^{\Delta}$	42.1 ± 4.7	41.5 ± 5.4	42.4 ± 4.1	0.23
Waist circumference (cm) $^{\Delta}$	118.8 ± 10.4	115.8 ± 10.4	120.2 ± 10.3	0.13
Sarcopenic Obesity, n (%)	145 (89.5)	59 (93.7)	86 (86.9)	0.17
SBP (mmHg) $^{\Delta}$	140.7 ± 15.5	146.8 ± 13.3	136.4 ± 15.5	< 0.001
DBP (mmHg) $^{\Delta}$	86.0 ± 10.7	85.9 ± 10.6	86.2 ± 10.8	0.33
Menopause, n (%)	80 (49.4)	34 (54.0)	46 (56.5)	0.35
DM2, n (%)	52 (32.7)	19 (31.51)	33 (33.7)	0.74
HT, n (%)	114 (87.7)	46 (90.2)	68 (86.1)	0.49
Dyslipidemia, n (%)	128 (81.0)	49 (81.7)	79 (80.6)	0.87
Osteopenia n (%)	34 (21.0%)	15 (23.8)	19 (19.2)	0.48

$^{\Delta}$ Data are expressed as mean ± SD. Abbreviations: *BMI* body mass index, *RYGB* roux-en-Y gastric bypass, *SG* vertical sleeve gastrectomy, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *DM2* type 2 diabetes, *HT* hypertension

Table 2 Comparative analysis of anthropometric parameters, blood pressure and body composition at baseline and the variation of parameters one and two years after BS

Variable	Baseline				Variation one year after BS				Variation two years after BS			
	Overall ($n=162$)	SG ($n=63$)	RYGB ($n=99$)	*P* value	SG ($n=60$)	RYGB ($n=95$)	*P* value	*P* adjust.	SG ($n=45$)	RYGB ($n=85$)	*P* value	*P* adjust.
Weight (kg)	108.2 ± 13.5	107.0 ± 15.6	109.1 ± 11.9	0.13	-35.6 ± 12.7	-39.1 ± 8.3	0.041	0.12	-36.6 ± 14.4	-41.2 ± 10.2	0.031	0.029
BMI (kg/m^2)	42.1 ± 4.7	41.5 ± 5.4	42.4 ± 4.1	0.34	-13.8 ± 4.8	-15.2 ± 3.3	0.027	0.07	-14.1 ± 5.6	-16.1 ± 4.0	0.002	0.021
SBP (mmHg)	140.7 ± 15.5	146.8 ± 13.3	136.4 ± 15.5	< 0.001	-20.7 ± 18.7	-11.4 ± 22.2	0.16	0.13	-15.2 ± 15.1	-9.7 ± 22.8	0.47	0.31
DBP (mmHg)	86.0 ± 10.7	85.9 ± 10.6	86.2 ± 10.8	0.33	-15.2 ± 19.2	-15.0 ± 15.6	0.96	0.97	-7.4 ± 13.6	-14.8 ± 15.3	0.17	0.15
BMC (g)	2.59 ± 0.32	2.56 ± 0.30	2.61 ± 0.34	0.26	-0.12 ± 0.14	-0.19 ± 0.11	< 0.001	0.004	-0.20 ± 0.12	-0.31 ± 0.14	< 0.001	< 0.001
Body fat mass (kg)	54.1 ± 8.6	52.8 ± 9.9	55.0 ± 7.6	0.10	-26.6 ± 9.5	-31.9 ± 7.3	< 0.001	< 0.001	-26.4 ± 11.3	-32.6 ± 7.9	< 0.001	0.004
Total body fat (%)	52.0 ± 3.4	51.5 ± 3.7	52.3 ± 3.2	0.17	-14.4 ± 6.1	-18.3 ± 6.4	< 0.001	0.005	-13.1 ± 7.2	-18.4 ± 6.1	< 0.001	< 0.001
Trunk fat (%)	55.8 ± 3.8	54.8 ± 4.5	56.3 ± 3.2	0.013	-17.7 ± 7.7	-23.2 ± 8.1	< 0.001	0.001	-16.9 ± 8.9	-24.5 ± 8.1	< 0.001	< 0.001
Legs fat (%)	49.1 ± 5.4	49.3 ± 4.9	48.9 ± 5.7	0.68	-10.9 ± 5.2	-13.1 ± 5.4	0.01	0.13	-8.9 ± 6.3	-12.7 ± 6.7	0.002	0.033
Total lean mass (kg)	49.7 ± 5.8	49.2 ± 5.9	50.0 ± 5.7	0.41	-6.3 ± 3.4	-6.3 ± 2.9	1.00	0.38	-7.4 ± 3.4	-7.4 ± 3.0	0.91	0.11
Arms lean mass (kg)	5.5 ± 1.2	5.5 ± 1.1	5.5 ± 1.3	0.98	-0.6 ± 1.0	-0.8 ± 1.0	0.20	0.31	-0.7 ± 1.0	-0.9 ± 1.0	0.50	0.87
Legs lean mass (kg)	17.4 ± 2.6	17.0 ± 2.6	17.7 ± 2.5	0.11	-3.0 ± 1.4	-3.4 ± 1.5	0.07	0.28	-3.5 ± 1.6	-3.9 ± 1.4	0.17	0.92
L1-L4 BMD (g/cm^2)	1.24 ± 0.15	1.24 ± 0.15	1.24 ± 0.15	0.69	-0.06 ± 0.06	-0.06 ± 0.07	0.93	0.89	-0.08 ± 0.09	-0.10 ± 0.08	0.07	0.16
L1-L4 T-score	0.40 [-0.40, 1.10]	0.40 [-0.50, 1.10]	0.40 [-0.40, 1.10]	0.80	-0.41 ± 0.52	-0.44 ± 0.56	0.72	0.35	-0.57 ± 0.72	-0.83 ± 0.63	0.037	0.09
L1-L4 Z-score	0.00 [-0.80, 0.80]	0.10 [-0.90, 0.90]	-0.10 [-0.80, 0.70]	0.49	0.53 ± 0.52	0.66 ± 0.60	0.22	0.37	0.43 ± 0.65	0.43 ± 0.62	0.98	0.86
Femoral neck BMD (g/cm^2)	1.04 ± 0.13	1.02 ± 0.14	1.04 ± 0.12	0.35	-0.07 ± 0.07	-0.08 ± 0.07	0.35	0.32	-0.09 ± 0.07	-0.12 ± 0.07	0.041	0.049
Femoral neck T-score	0.40 [-0.40, 1.30]	0.40 [-0.70, 1.30]	0.50 [-0.20, 1.30]	0.34	-0.61 ± 0.62	-0.70 ± 0.53	0.36	0.29	-0.78 ± 0.60	-1.02 ± 0.62	0.035	0.044
Femoral neck Z-score	0.20 [-0.60, 0.80]	0.20 [-0.60, 0.80]	0.10 [-0.50, 0.90]	0.81	0.10 ± 0.63	0.10 ± 0.60	0.97	0.81	-0.04 ± 0.61	-0.06 ± 0.65	0.87	0.54
Total femur BMD (g/cm^2)	1.15 ± 0.14	1.15 ± 0.14	1.20 ± 0.13	0.033	-0.09 ± 0.06	-0.13 ± 0.06	< 0.001	0.003	-0.13 ± 0.08	-0.18 ± 0.08	0.002	0.010
Total femur T-score	1.60 [0.70, 2.40]	1.40 [0.40, 2.10]	1.60 [1.00, 2.50]	0.09	-0.77 ± 0.49	-1.03 ± 0.47	0.001	0.004	-1.10 ± 0.62	-1.48 ± 0.65	0.001	0.008
Total femur Z-score	1.00 [0.40, 1.70]	1.00 [0.20, 1.60]	1.00 [0.40, 1.80]	0.25	-0.07 ± 0.46	-0.24 ± 0.50	0.034	0.057	-0.37 ± 0.67	-0.59 ± 0.60	0.06	0.07
Total body BMD (g/cm^2)	1.25 ± 0.11	1.24 ± 0.10	1.26 ± 0.11	0.17	0.04 ± 0.05	-0.06 ± 0.05	0.10	0.15	-0.11 ± 0.15	-0.12 ± 0.07	0.48	0.74
Total body T-score	1.80 [1.10, 2.70]	1.80 [1.00, 2.60]	1.80 [1.20, 2.70]	0.42	-0.43 ± 0.50	-0.56 ± 0.51	0.12	0.18	-0.87 ± 0.64	-1.23 ± 0.64	0.003	0.014
Total body Z-score	0.50 [-0.10, 1.20]	0.50 [-0.20, 1.20]	0.50 [-0.10, 1.20]	0.78	0.70 ± 0.66	0.72 ± 0.66	0.85	0.93	0.27 ± 0.73	0.21 ± 0.71	0.60	0.57
FRAX® major	1.40 [1.00, 2.30]	1.30 [1.00, 2.70]	1.40 [1.00, 2.30]	0.63	0.78 ± 1.13	0.64 ± 0.88	0.40	0.81	0.84 ± 1.37	0.98 ± 1.35	0.60	0.49
FRAX® hip	0.00 [0.00, 0.10]	0.0 [0.00, 0.30]	0.00 [0.00, 0.10]	0.17	0.09 ± 0.76	0.17 ± 0.45	0.43	0.21	0.09 ± 0.90	0.31 ± 0.69	0.13	0.21

All data in this table are expressed as mean ± SD or median [Min, Max]. Abbreviations: *BS* bariatric surgery, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMC* bone mineral content, *L1-L4* lumbar spine from 1 to 4, *BMD* bone mineral density

Table 3 Comparative analysis of laboratory parameters at baseline, and their variation one and two years after BS

Variable	Baseline				Variation one year after BS				Variation two years after BS			
	Overall sample (n=162)	SG (n=63)	RYGB (n=99)	P value	SG (n=60)	RYGB (n=95)	P value	P adj.	SG (n=45)	RYGB (n=85)	P value	P adj.
Phosphocalcium and bone metabolism markers												
25-OH-Vitamin D (ng/mL)	18.0 [13.0, 22.0]	17.5 [13.5, 21.5]	19.0 [13.0, 23.0]	0.43	13.1±12.6	7.8±12.8	0.013	0.014	11.9±11.0	9.5±14.4	0.34	0.20
Vitamin D insuf. n, (%)*	141 (89.2)	55 (91.7)	86 (87.8)	0.44	28 (46.7)	62 (65.2)	0.038	0.063	23 (51.1)	54 (63.5)	0.22	0.13
P+ (mg/dL)	3.4±0.5	3.3±0.4	3.4±0.5	0.24	0.5±0.6	0.5±0.6	0.84	0.94	0.4±0.5	0.4±0.7	0.46	0.91
Mg (mEq/L)	1.6±0.1	1.6±0.1	1.6±0.1	0.36	0.0±0.1	0.0±0.1	0.044	0.07	0.0±0.1	0.5±4.1	0.43	0.018
Corrected Ca (mg/dL)	9.36±0.31	9.44±0.29	9.30±0.31	0.007	0.19±0.69	0.14±0.39	0.62	0.71	0.03±0.38	-0.02±0.61	0.95	0.60
PTH (pg/mL)	55.0±20.8	54.6±18.9	55.2±22.0	0.84	-6.3±18.6	-2.3±21.5	0.24	0.35	9.5±23.5	3.9±26.6	0.24	0.56
Osteocalin (ng/mL)	16.6±5.5	17.5±5.1	16.0±5.7	0.12	17.5±11.1	24.0±13.1	0.003	<0.001	18.0±11.8	26.8±16.1	0.003	0.013
CTX (µg/L)	0.29 [0.21, 0.38]	0.32 [0.24, 0.40]	0.27 [0.19, 0.36]	0.07	0.46±0.22	0.62±0.26	< 0.001	< 0.001	0.36±0.23	0.61±0.87	0.07	0.011
24h U calcium (mEq/24 h)	7.4 [4.7, 10.4]	8.2 [4.8, 10.1]	6.7 [4.7, 11.1]	0.68	0.3±4.5	-2.1±4.5	0.003	0.011	0.5±3.6	-1.7±4.5	0.014	0.018
Other parameters												
STP (g/L)	70.7±4.4	70.3±3.8	70.9±4.8	0.48	-3.4±3.9	-4.1±4.2	0.31	0.37	0.6±16.0	-4.0±4.7	0.014	0.017
HbA1c (%)	5.9±0.9	5.8±0.9	6.0±0.9	0.08	-0.4±0.6	-0.7±0.8	0.018	0.006	-0.3±0.4	-0.4±2.4	0.80	0.83
LDL (mg/dL)	113.7±34.9	117.6±29.3	111.3±38.0	0.28	-9.4±31.2	-23.0±32.9	0.011	0.025	-8.3±31.1	-21.0±42.1	0.07	0.10
GGT (U/L)	26.0 [19.0, 39.0]	25.0 [17.0, 37.0]	26.0 [20.0, 39.0]	0.39	-11.0±15.5	-17.7±71.9	0.47	0.48	-3.1±30.6	-14.7±88.6	0.38	0.83
ALP (U/L)	80.8±21.5	81.1±19.7	80.5±22.6	0.86	-9.2±18.3	3.1±18.7	<0.001	<0.001	-6.0±19.6	1.6±23.7	0.06	0.06
AST (U/L)	20.0 [17.0, 26.0]	20.0 [18.0, 22.0]	21.0 [17.0,28.0]	0.08	-1.5±9.1	5.2±17.2	0.006	0.006	-1.2±8.3	3.6±13.0	0.025	0.06
ALT (U/L)	22.0 [17.0, 29.0]	21.0 [17.0, 26.0]	23.0 [17.0, 32.0]	0.07	-4.5±10.3	5.6±29.7	0.012	0.007	-4.5±9.4	2.8±20.1	0.020	0.033
eGFR (mL/min/1.73m^2)	102.5±13.5	102.0±13.5	102.9±13.5	0.71	-2.1±11.0	0.4±9.0	0.12	0.11	-4.2±15.8	0.2±12.8	0.08	0.17
Microalbuminuria (mg/L)	8.4 [4.7, 21.0]	7.0 [4.7, 13.7]	9.6 [4.6, 23.8]	0.14	-23.5±118.1	-11.2±65.6	0.41	0.40	-3.5±164.0	-8.5±111.0	0.84	0.77
Iron (µg/dL)	72.0 [56.0, 89.0]	72.5 [54.0, 89.0]	71.0 [57.0, 89.0]	0.97	16.9±39.8	9.4±31.0	0.20	0.13	23.8±31.1	24.8±40.0	0.88	0.97
Transferrin (mg/dL)	275.3±42.0	275.3±38.9	275.3±44.0	0.99	-55.4±43.2	-27.5±43.0	<0.001	<0.001	-35.5±35.1	-15.9±57.8	0.04	0.06
Ferritin (ng/mL)	81.0 [40.1, 177.9]	72.0[37.3, 177.9]	101.7 [40.1, 179.8]	0.56	42.9±71.4	8.7±90.7	0.016	0.012	11.3±55.2	-13.5±97.0	0.12	0.12
Folic acid (ng/mL)	5.7 [4.4, 8.0]	5.2 [4.3, 7.2]	6.2 [4.5, 8.4]	0.11	4.6±4.8	5.3±5.7	0.48	0.68	3.9±4.8	4.3±5.3	0.68	0.66
Vitamin B12 (pg/mL)	358 [285, 449]	343 [285, 441]	364 [285, 457]	0.58	-9.4±135.4	-56.3±208.1	0.13	0.005	74.2±291.3	-41.5±282.4	0.029	0.034
TSH (µUI/mL)	1.8±1.2	1.6±0.7	1.9±1.5	0.09	-0.3±0.8	-0.3±1.5	0.70	0.70	-0.1±0.6	-0.3±0.7	0.19	0.19
Total bile acids (µmol/L)	2.2 [1.3, 3.5]	2.1 [1.4, 3.4]	2.3 [1.3, 3.5]	0.61	0.0±5.2	1.5±3.9	0.06	0.13	-0.0±2.1	2.0±4.8	0.014	0.023

Table 3 (continued)

Variable	Baseline				Variation one year after BS				Variation two years after BS			
	Overall sample ($n=162$)	SG ($n=63$)	RYGB ($n=99$)	*P* value	SG ($n=60$)	RYGB ($n=95$)	*P* value	*P* adj.	SG ($n=45$)	RYGB ($n=85$)	*P* value	*P* adj.
Vit E (µg/mL)	11.7±3.3	12.2±3.2	11.4±3.3	0.16	0.1±3.4	-0.9±3.8	0.10	0.12	0.1±4.0	-0.9±4.0	0.20	0.13
Vit C (µg/mL)	34.4±7.6	36.4±8.4	33.3±6.9	0.016	-2.3±11.5	-2.2±7.2	0.95	0.69	-3.0±8.5	-2.1±7.3	0.53	0.59

All data in this table are expressed as mean ± SD or median [Min, Max]. *BS* bariatric surgery, *STP* serum total protein, *HbA1c* hemoglobin A1c, *LDL* low-density lipoprotein cholesterol, *TG* triglycerides, *GGT* gamma-glutamyltransferase, *ALP* alkaline phosphatase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *eGFR* estimated glomerular filtration rate, *P+* phosphorus, Corrected Ca albumin-corrected plasmatic calcium, *Mg* magnesium, *PTH* parathyroid hormone, *CTX* s-carboxy-terminal cross-linked telopeptide type 1 collagen, *TSH* thyroid-stimulating hormone. *Vit D insufficiency refers to the prevalence of this condition in the presented timepoint and not to a variation

differences between groups regarding supplementation with vitamin D, magnesium, or calcium before or after surgery (Supplementary table C).

Baseline predictors for BMD variation after surgery

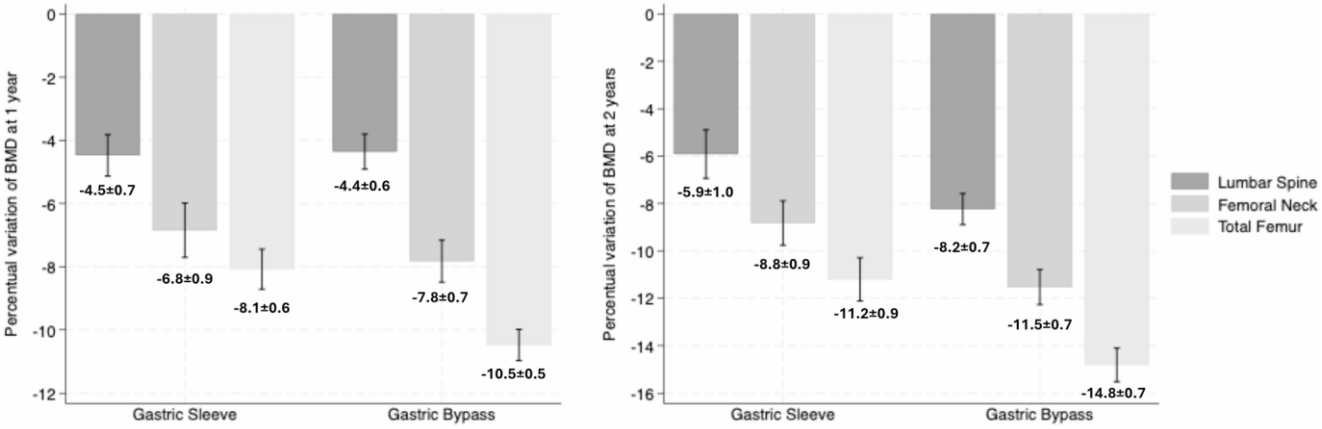
Evaluation of the predictors of BMD variation of total femur, femoral neck and lumbar spine two years after surgery is presented in Table 4. We found that RYGB was a predictor of BMD reductions in all these three areas, even after adjusting for age. Menopause at baseline was correlated with lower total femur BMD two years after BS [β=-0.54 (-0.84 to -0.24), $p = 0.001$] while higher osteocalcin levels at baseline were correlated with greater reductions in femoral neck at this time point [β=-0.02 (-0.05 to -0.00), $p = 0.036$]. Higher BMD at baseline in a specific region (total femur/femoral neck/lumbar spine) was predictor of higher BMD loss at the corresponding site.

Logistic regression showed that older age predicted osteoporosis/osteopenia 2 years after BS, whereas higher baseline BMC was protective. RYGB also showed a trend towards predicting this outcome (Supplementary table D).

Discussion

In the present study, we show that BS induced several changes in BMD at various sites and in body composition during the two years of follow-up, that were more noticeable in the RYGB group.

Regarding BMD variations, the hip was the area that presented more differences according to the type of surgery performed, with greater reductions in total femur BMD after RYGB both at one and two years after BS. Femoral neck was the second area to show differences, that became apparent two years after surgery, also with higher decreases in the group submitted to RYGB (Fig. 1). These findings are in accordance with a recent study by Gómez-Vaquero et al. with a 12-month follow-up, that detected higher BMD losses after RYGB than SG, more pronounced in the total femur (-9.95% vs. -6.20%) and femoral neck (-6.39 vs. -3.31%) [15]. The latest meta-analysis addressing the short-term effects of BS on bone also concluded that patients undergoing RYGB presented greater reductions in BMD than those after SG at the femoral neck, lumbar spine, and total hip one year after surgery, while two years after BS only total hip remained with lower BMD, which strengthens a seemingly greater impact of RYGB on hip bone BMD, as shown by our study [10]. This bone loss after RYGB was also observed in other study evaluating volumetric bone mineral density (vBMD), with significant vBMD loss at the total femur, lumbar spine, radius, and tibia. Importantly, there was an estimated annual



Bone mineral Density, g/cm²	Baseline (n=162)	1 year (n=156)	2 years (n=130)
Lumbar Spine	**1.24 ± 0.15**	**1.18 ± 0.15***	**1.15 ± 0.16*Δ**
Gastric Sleeve	1.23 ± 0.15	1.17 ± 0.15*	1.18 ± 0.16*Δ
Gastric Bypass	1.24 ± 0.15	1.19 ± 0.15*	1.13 ± 0.15*Δ
Femoral Neck	**1.04 ± 0.13**	**0.95 ± 0.12***	**0.93 ± 0.12*Δ**
Gastric Sleeve	1.02 ± 0.14	0.95 ± 0.13*	0.95 ± 0.13*Δ
Gastric Bypass	1.04 ± 0.13	0.96 ± 0.11*	0.91 ± 0.11*Δ
Total Femur	**1.18 ± 0.14**	**1.07 ± 0.13***	**1.03 ± 0.13*Δ**
Gastric Sleeve	1.15 ± 0.14	1.06 ± 0.15*	1.05 ± 0.13*Δ
Gastric Bypass	1.20 ± 0.13	1.07 ± 0.13*	1.01 ± 0.13*Δ

Fig. 1 Comparative analysis of the percentual BMD variation (mean ± SE) on lumbar spine, femoral neck or total femur one ($n = 156$) and two years ($n = 130$) after BS according to surgical technique at different bone areas. Paired t-tests were performed to compare overall bone mineral density on lumbar spine, femoral neck or total femur between the baseline and 1 and 2 years post-BS. Abbreviations: BMD, bone mineral density; SE, standard error; BS, bariatric surgery

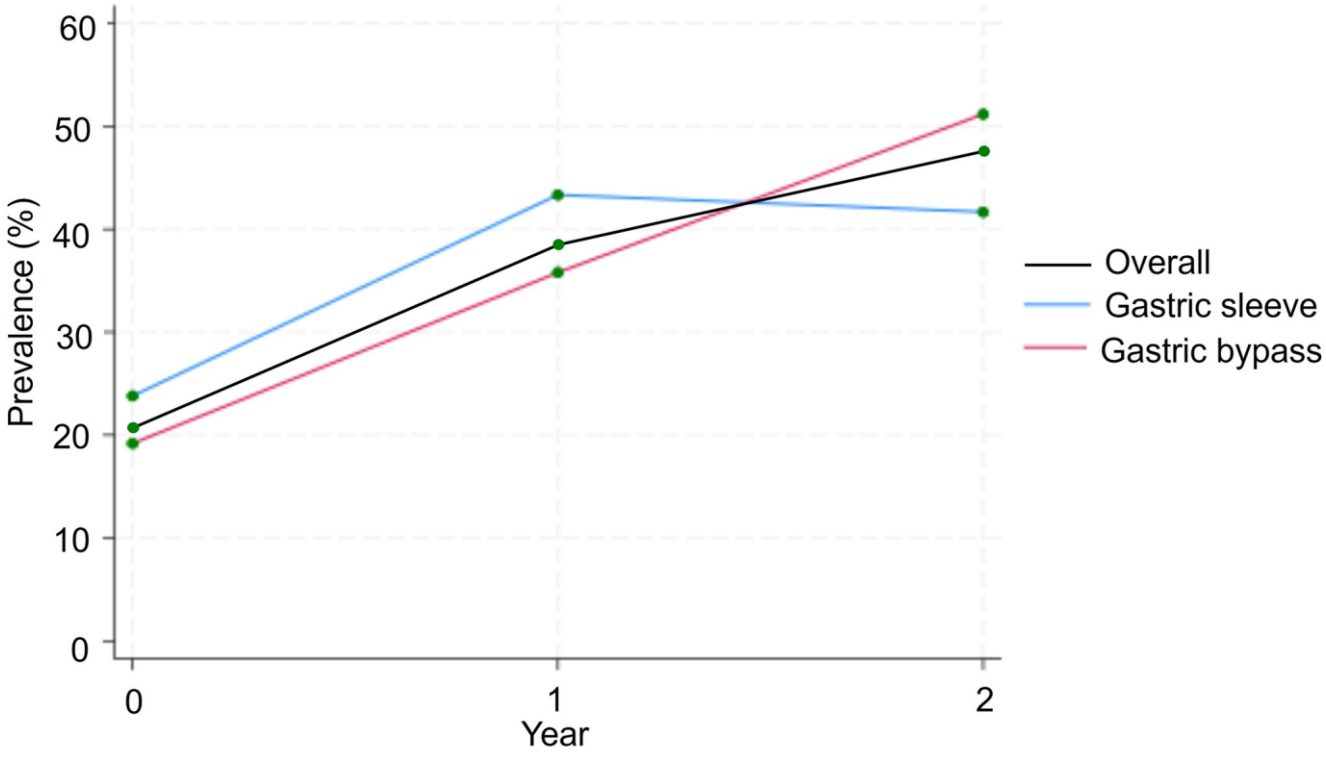
vBMD loss of 5.0% at the LS, 2.8% at the radius, and 2.7% at the tibia during the assessed follow-up time after RYGB [16]. The need to tackle this issue, associated with osteoporosis and increased fracture risk, led to the elaboration of European guidelines (ECTS 2022) for the prevention and treatment of osteoporosis secondary to bariatric surgery [17].

The findings of our study become even more relevant when viewed in perspective. According to previous data, mean BMD loss after two years among females with 50–59 years (not submitted to BS, with no medication or diseases known to affect bone) was − 1.9% for total hip and − 2.1% for lumbar spine [18]. Another study found that early postmenopausal years were associated with annual BMD reductions of 1.8–2.3% in the spine and 1.0–1.4% in the hip [19]. Before menopause, the rate of BMD loss was lower in both studies as expected. Our study found a BMD reduction of -14.8% in total hip and − 8.2% in lumbar spine two years after RYGB and reductions of -11.2% and − 5.2%, respectively, after SG (Fig. 2).

Regarding bone metabolism markers, our study found a steeper increase of osteocalcin and CTX after RYGB (Supplementary Fig. 2), with no differences between surgical techniques regarding calcium levels variation after BS. These two findings are similar to those of a recent meta-analysis including 8 studies that, contrary to our work, found no differences in CTX variation after BS [20]. The role of bone turnover makers such as osteocalcin or CTX as a predictor of fractures has been previously exposed [21], with our study showing an agreement between increased bone formation and resorption markers with reduced BMD after surgery. Interestingly, unlike previous papers [20], we found no differences between SG and RYGB in PTH levels variation after surgery, indicating that BMD reductions may be explained by other players.

We also concluded that 24-hour urinary calcium diminished after RYGB and increased slightly after SG. This reduction after RYGB is demonstrated in other studies and may be interpreted as a way to spare calcium, whose absorption is impaired in the gastrointestinal tract [22]. In addition, it may also indicate that calcium supplementation should be optimized among these patients (Supplementary table C).

Despite a slightly increased risk of fracture according to FRAX, one and two years after BS, there were no differences between groups. According to a recent meta-analysis, fracture risk following BS seems to increase after hypoabsorptive techniques, while this risk remains stable after restrictive procedures at a mean/median follow-up > 24 months [23]. Considering this data, a 2-year follow-up period was likely insufficient to adequately assess this outcome.



	Baseline (n=162)	1 year (n=155)	2 years (n=134)
Osteopenia or osteoporosis, n(%)	34 (21.0)	60 (38.7)*	64 (47.8)*Δ

Fig. 2 Evolution of the prevalence of osteopenia and osteoporosis after BS according to surgery type. Participants diagnosed with osteoporosis at 12 months ($n = 4$) were also considered to have osteoporosis at 24 months. McNemar tests were used to compare the prevalence of osteopenia or osteoporosis between the baseline and 1- and 2-years post-BS. *$p < 0.01$ in comparison to the baseline. Δ$p < 0.01$ in comparison to 1-year post-BS. Abbreviations: BS, bariatric surgery

Regarding body composition, our study found that RYGB induced a greater body fat mass reduction (which occurred in the different evaluated sites by DXA), presenting a similar lean mass loss when compared to SG. These findings are reassuring since lean mass is mainly composed by muscle, an organ with important metabolic and functional roles [24]. Conversely, the available evidence has not presented clinically different changes in body composition between these two surgical techniques in the short- or long-term [25, 26].

Other interesting finding is that TBA increase after RYGB, remaining stable after SG, similar to findings in other studies [27]. Recent evidence supports their important metabolic effects on lipid and glucose homeostasis, also influencing gut microbiota after BS [28]. Furthermore, bile acids play a role in bone metabolism, by favoring bone formation under normal circumstances, while excessive or low levels tend to promote bone resorption [29]. The only study correlating bile acid levels and BMD after BS performed in a cohort of Chinese individuals, found that TBA were positively correlated with femoral neck BMD. In contrast, another study from Yang S. and colleagues found that TBA were linked with higher risk for abnormal bone metabolism and decreased BMD among patients with diabetes mellitus [30].

Our study faced some limitations. This is an observational non-randomized study which may have introduced selection bias. Despite this fact, there were no statistically significant differences between groups at baseline, apart from SBP (Table 1). We did not include male patients due to the scarcity of these individuals undergoing BS at our center (only 15% males vs. 85% females), which could compromise robust conclusions regarding the impact of surgery in this sex. Certain variables such as SBP, DBP and waist circumference displayed high missing rates (> 50%) at baseline and during follow-up. This is mainly explained by COVID-19 pandemic, which disrupted follow-up consultations essential for these assessments. The low number of subjects presenting these data may explain the unexpected differences in SBP (higher in the SG group) observed at baseline. Although targeting specifically women aged 40 years or older could potentially limit the generalizability of our findings, we do not regard this inclusion criterion as a

Table 4 Linear regression analysis with the baseline predictors of BMD variation in different bone areas 2 years after surgery

Baseline predictors	BMD variation - total femur		BMD variation - femoral neck		BMD variation - lumbar spine	
	β (95% CI)	P value*	β (95% CI)	P value*	β (95% CI)	P value*
BMI	0.01 (-0.01 to 0.04)	0.31	0.00 (-0.02 to 0.02)	0.99	-0.01 (-0.04 to 0.01)	0.26
Age	-0.01 (-0.02 to 0.01)	0.39	0.00 (-0.01 to 0.02)	0.73	-0.01 (-0.03 to 0.01)	0.24
Menopause	-0.54 (-0.84 to -0.24)	0.001	-0.12 (-0.42 to 0.18)	0.43	-0.23 (-0.55 to 0.09)	0.17
RYGB	-0.39 (-0.62 to -0.15)	0.001	-0.24 (-0.47 to -0.02)	0.036	-0.26 (-0.50 to -0.02)	0.034
Vitamin D insufficiency	0.09 (-0.27 to 0.46)	0.613	-0.32 (-1.21 to 0.58)	0.49	0.28 (-0.09 to 0.65)	0.132
Corrected Ca	-0.10 (-0.49 to 0.28)	0.60	0.07 (-0.30 to 0.45)	0.69	0.10 (-0.30 to 0.50)	0.62
Osteocalcin	0.00 (-0.03 to 0.02)	0.83	-0.02 (-0.05 to -0.00)	0.036	-0.01 (-0.04 to 0.01)	0.30
CTX	-0.47 (-1.34 to 0.40)	0.29	-0.47 (-1.34 to 0.40)	0.28	-0.53 (-1.48 to 0.41)	0.26
PTH	0.00 (-0.01 to 0.01)	0.99	0.00 (0.00 to 0.01)	0.41	0.00 (-0.00 to 0.01)	0.58
Bile acids	0.04 (-0.01 to 0.09)	0.14	0.01 (-0.04 to 0.06)	0.67	0.03 (-0.03 to 0.08)	0.31
24-urine Calcium	-0.02 (-0.04 to 0.01)	0.28	-0.02 (-0.05 to 0.01)	0.15	-0.03 (-0.06 to 0.00)	0.086
BMD lumbar spine	-0.12 (-0.88 to 0.64)	0.76	-0.57 (-1.30 to 0.16)	0.12	-0.85 (-1.63 to -0.08)	0.031
BMD total femur	-1.77 (-2.55 to -0.99)	<0.001	-1.49 (-2.26 to -0.73)	<0.001	0.79 (-0.07 to 1.65)	0.072
BMD femoral neck	-1.01 (-1.87 to -0.15)	0.022	-2.66 (-3.37 to -1.96)	<0.001	0.36 (-0.55 to 1.27)	0.44
BMC	-0.21 (-0.60 to 0.17)	0.27	-0.15 (-0.52 to 0.22)	0.42	-0.03 (-0.43 to 0.37)	0.88
Total lean mass	0.00 (-0.02 to 0.02)	0.73	-0.01 (-0.02 to 0.01)	0.57	0.00 (-0.02 to 0.02)	0.72
Total Fat mass	0.01 (-0.01 to 0.02)	0.73	0.01 (0.0 to 0.02)	0.077	0.01 (-0.01 to 0.02)	0.42

**P* value is adjusted for age and surgery type, except gastric bypass (only adjusted for age) and age (only adjusted for surgery type). Corrected *Ca* albumin-corrected plasmatic calcium, *P+* phosphorus, *Mg* magnesium, *PTH* parathyroid hormone, *CTX* s-carboxy-terminal cross-linked telopeptide type 1 collagen

major limitation, since it was necessary due to validation constraints inherent to the FRAX® tool. Moreover, a recent meta-analysis showed that the group of subjects with more than 40 years had a lower BMD at the lumbar spine and femoral neck following bariatric surgery when compared with younger subjects [31]. For this reason and considering the various risk factors that tend to aggregate among older subjects, the authors believe that this is precisely the group that needs more evidence to eventually guide further intervention. The lack of systematic calcium supplementation (recommended in most guidelines), may have amplified the true effects of bariatric surgery on bone metabolism observed in this study, especially after RYGB. This approach was initially motivated by the existence of previous studies [32] and meta-analysis [33] suggesting a potential link between calcium supplementation and increased CV risk. However, this practice was revised after evaluating the results of this paper (and after various recent meta-analysis [34, 35] have refuted the previously reported data regarding CV risk). The lack of systematic calcium supplementation in some centres reinforces the importance of calcium, vitamin D and protein intake, that tend to be lower among eastern diets [36]. Studies in Chinese cohorts, for example, have shown that vitamin D and calcium intake after bariatric surgery frequently remain below recommended levels, with a very high prevalence of vitamin D deficiency (up to 91.7% at 12 months). The traditional Chinese dietary pattern, which relies heavily on rice and wheat-based foods, may contribute to difficulties in adhering to the relatively low-carbohydrate, high protein dietary regimen [37]. These facts, associated with the paucity of data regarding bariatric surgery impact on bone health among Asian cohorts, shed light on the importance of the specific diets after bariatric surgery and are potential topics for further studies.

Due to reasons beyond our control, a larger proportion of patients was submitted to SG later than those who underwent RYGB. This implied that the follow-up of these particular patients demanded more time to complete the two years. Due to scheduling constraints, 2-year outcomes were missing for a small number of patients (predominantly in the SG group), accounting for the imbalance in attrition from baseline to the 2-year follow-up between groups. Most of these patients continue in the BARIATRIC BONE project and will continue to be followed for up to 10 years after surgery.

Despite its limitations, this paper is, to our knowledge, the largest prospective study to date comparing directly the impact of RYGB and SG in bone metabolism. In addition, it also presents a follow-up of 2 years and comprehensive evaluation of the body composition by DXA.

Conclusion

RYGB presented a greater impact in bone metabolism and body composition than SG two years after surgery, with a greater decline in the BMD of the femoral neck and total femur as well as greater loss in body fat mass, without differences in lean mass loss. These BMD changes were accompanied by a greater rise in bone turnover markers (osteocalcin and CTX) after RYGB. Evaluation of 24-hour

urinary calcium showed a decrease of its levels after this hypoabsorptive technique, which may be explained by deficient calcium supplementation. More prospective studies are needed to further clarify these findings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11695-026-08672-8.

Author contributions Fernando Mendonça: investigation, project administration, supervision, writing - original draft; Ana R. Leite and João S. Neves – Data curation, formal analysis and visualization, writing – review and editing ; Pietra Soares and Mafalda Maia, Carla Luís, Ilda Rodrigues, Liliana Carvalho, Joana Alves, Beatriz Fonseca, Beatriz Sá Pinto, Beatriz Silva, Joana Barbosa, Luísa Couto, Telma Moreno, Marta Canha: investigation, writing – review and editing; Jorge Pedro, Diana Festas, Ana Varela, Ana Oliveira, Teresa Faria, Ana Fernandes, Sónia Vieira, Altin Ndrio, João-Tiago Guimarães, Eduardo L Costa, CRIO group: resources, writing – review and editing; Raquel Soares and Paula Freitas: conceptualization, investigation, methodology, resources.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data Availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Competing interests The authors declare no competing interests.

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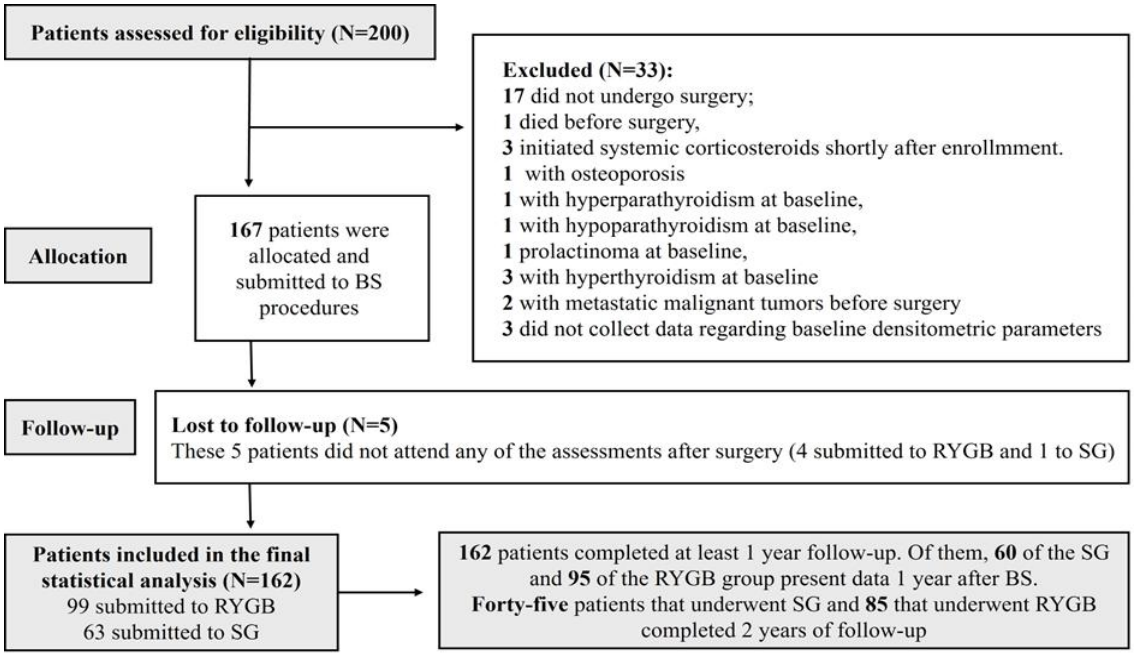
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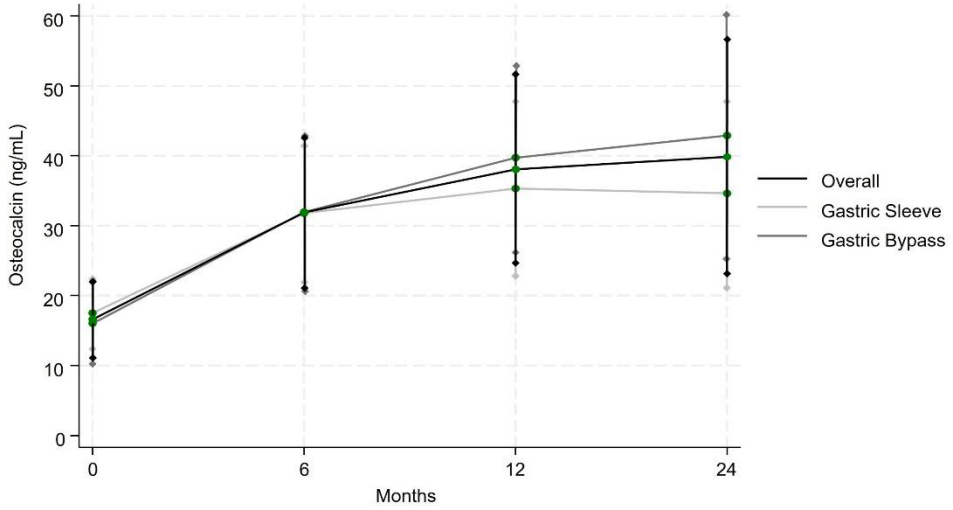
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Supplementary material

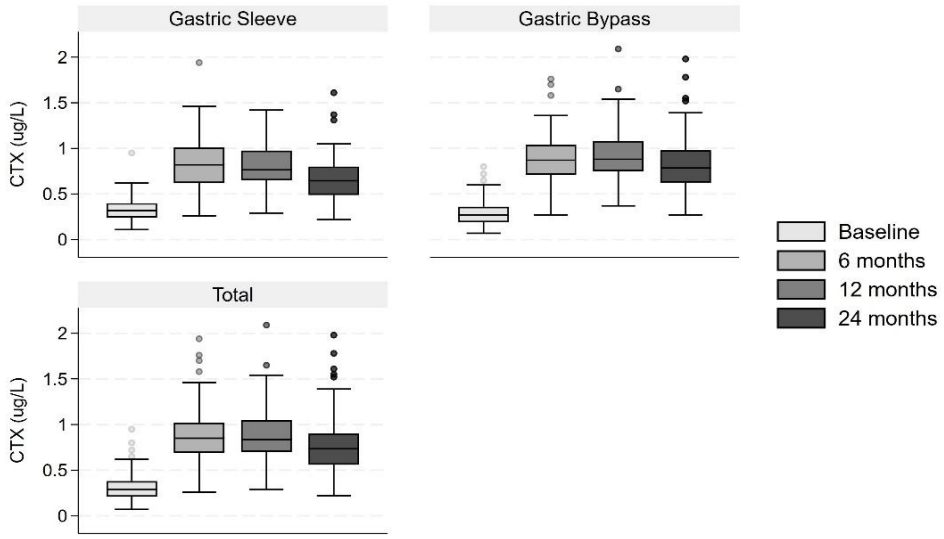


Supplementary image 1: Flowchart of patient`s recruitment to this study.



	Baseline (n=144)	6 months (n=153)	12 months (n=158)	24 months (n=127)
Overall	16.60 ± 5.54	31.89 ± 10.73*	38.04 ± 13.39*Δ	39.84 ± 16.76*Δ
Gastric Sleeve	17.50 ± 5.15	31.79 ± 9.93*	35.30 ± 12.61*Δ	34.62 ± 13.41*
Gastric Bypass	16.02 ± 5.73	31.95 ± 11.26*	39.72 ± 13.64*Δ	42.90 ± 17.82*Δ

Supplementary image 2. Comparative analysis of osteocalcin levels at baseline, six months, one and two years after BS. Paired t tests were performed to compare osteocalcin levels between the baseline and the different timepoints evaluated post-BS. *p<0.001 in comparison to baseline. Δp<0.001 in comparison to 6 months post-BS. Abbreviations: BS, bariatric surgery.



	Baseline (n=162)	6 months (n=146)	12 months (n=158)	24 months (n=126)
Overall	0.29 [0.21, 0.38]	0.85 [0.69, 1.02]*	0.84 [0.70, 1.05]*	0.74 [0.56, 0.90]*$^{\Delta\delta}$
Gastric Sleeve	0.32 [0.24, 0.40]	0.82 [0.62, 1.01]*	0.77 [0.65, 0.97]*	0.65 [0.49, 0.80]*$^{\Delta\delta}$
Gastric Bypass	0.27 [0.19, 0.36]	0.87 [0.71, 1.04]*	0.88 [0.75, 1.08]*	0.79 [0.62, 0.98]*$^{\Delta\delta}$

Supplementary image 2. Comparative analysis of betacrosslaps-CTX levels at baseline, six months, one and two years after BS. Wilcoxon tests were performed to compare CTX levels between the baseline and the different timepoints evaluated post-BS. *p<0.001 in comparison to baseline. Δp<0.001 in comparison to 6 months post-BS. **δ** p<0.001 in comparison to 12 months post-BS. Abbreviations: CTX, s-carboxy-terminal cross-linked telopeptide type 1 collagen; BS, bariatric surgery.

Supplementary table A: Variation of parameters 6 months after surgery

	Baseline			**Six months after BS**			
	SG (n=63)	RYGB (n=99)	P value	SG	RYGB	P value	P adj.
Weight (kg)	107.0 ±15.6	109.1 ± 11.9	0.13	-29.0 ± 9.9	-30.1 ± 8.0	0.44	0.73
BMI (kg/m^2)	41.5 ± 5.4	42.4 ± 4.1	0.34	-11.2 ± 3.8	-11.71 ± 2.95	0.39	0.59
25-OH-Vitamin D (ng/mL)	17.5 [13.5, 21.5]	19.0 [13.0, 23.0]	0.43	10.6 ± 11.6	5.7 ± 11.7	**0.011**	**0.026**
P+ (mg/dL)	3.3 ± 0.4	3.4 ± 0.5	0.24	0.44 ± 0.48	0.36 ± 0.53	0.36	0.33
Mg (mEq/L)	1.6 ± 0.1	1.6 ± 0.1	0.36	0.02 ± 0.11	0.04 ± 0.12	0.55	0.63
Corrected Ca (mg/dL)	9.44 ± 0.29	9.30 ± 0.31	**0.007**	0.20 ± 0.34-	0.24 ± 0.32	0.42	0.46
PTH (pg/mL)	54.6 ± 18.9	55.2 ± 22.0	0.84	4.95 ± 20.37	-3.08 ± 22.49	0.61	0.34
Osteocalcin (ng/mL)	17.5 ± 5.1	16.0 ± 5.7	0.12	14.4 ± 9.4	16.6 ± 10.4	0.22	0.12
CTX (µg/L)	0.34 ± 0.15	0.30 ± 0.14	0.11	0.51 ± 0.25	0.60 ± 0.24	**0.038**	**0.020**
24h urine calcium (mEq/24h)	8.2 [4.8, 10.1]	6.7 [4.7, 11.1]	0.68	-0.74 ± 4.18	-2.34 ± 4.33	**0.048**	**0.059**

All data in this table are expressed as mean ± SD or median [Min, Max]. Abbreviations: *BS* bariatric surgery, *BMI* body mass index Corrected Ca albumin-corrected plasmatic calcium, P+ phosphorus, Mg magnesium, PTH parathyroid hormone, CTX s-carboxy-terminal cross-linked telopeptide type 1 collagen.

Supplementary table B: Assessment of comorbidity remission, prevalence of osteopenia/osteoporosis and sarcopenic obesity after BS

Variable	One-year after BS			Two-years after BS		
	SG	RYGB	P value	SG	RYGB	P value
DM2 Remission (%)	9 (47.9)	23 (67.9)	0.57	9 (75.0)	24 (82.8)	0.57
HT Remission (%)	8 (25.0)	22 (44.9)	0.07	5 (25.0)	13 (32.5)	0.55
Dyslipidemia Remission (%)	19 (38.8)	33 (41.8)	0.74	17 (47.2)	44 (62.0)	0.15
Osteopenia n, (%)	25 (41.7)	33 (34.7)	0.39	17 (37.8)	42 (49.4)	0.20
Cumulative Osteoporosis incidence (%)	3 (5.0)	1 (1.1)	0.13	3 (6.3)	6 (7.0)	0.87
Sarcopenic obesity (%)	6 (10.2)	4 (4.3)	0.55	6 (14.0)	5 (5.9)	0.38

Abbreviations: *BS* bariatric surgery, *HT* hypertension, *DM2* type 2 diabetes

Supplementary table C: Table of mineral and vitamin supplements

	Baseline			One year after BS			Two years after BS		
	SG (n=63)	RYGB (n=99)	P value	SG (n=63)	RYGB (n=99)	P value	SG	RYGB	P value
Multivitamin-mineral n, (%)	0 (0.0)	0 (0.0)	---	59 (93.6)	96 (97)	0.52	41 (85.4)	88 (96.7)	**0.014**
Iron, n (%)	0 (0.0)	1 (1.0)	0.42	8 (12.7)	20 (20.2)	0.32	3 (6.2)	16 (17.6)	0.16
Vitamin D, n (%)	4 (6.3)	1 (1.0)	0.06	18 (28.6)	40 (40.4)	0.11	16 (34.8)	33 (36.3)	0.86
Vitamin B12, n (%)	0 (0.0)	0 (0.0)	---	2 (3.2)	22 (22.2)	**< 0.001**	5 (10.4)	14 (15.6)	0.40
Mg, n (%)	2 (3.2)	0 (0.0)	0.07	5 (7.9)	11 (11.1)	0.50	5 (10.4)	16 (17.6)	0.26
Ca, n (%)	0 (0.0)	0 (0.0)	---	1 (1.6)	0 (0.0)	0.21	1 (2.1)	0 (0.0)	0.17

Abbreviations: *Mg* magnesium, *Ca* calcium

Supplementary table D: Logistic regression analysis with the baseline predictors of osteopenia/osteoporosis 2 years after surgery.

Baseline predictors	Osteopenia or osteoporosis	
	OR (95% CI)	P value*
BMI	1.04 (0.95-1.14)	0.36
Age	1.10 (1.03-1.18)	**0.006**
Menopause	1.11 (0.31-4.05)	0.87
RYGB	2.30 (0.86-6.13)	**0.096**
Vitamin D insufficiency	0.61 (0.16-2.30)	0.47
Corrected Ca	1.09 (0.24-5.03)	0.91
Osteocalcin	1.05 (0.96-1.15)	0.31
CTX	3.75 (0.09-150.99)	0.48
PTH	1.02 (0.99-1.04)	0.20
Bile acids	1.05 (0.87-1.27)	0.60
24-urine Calcium	0.95 (0.85-1.07)	0.43
BMC	0.01 (0.00-0.14)	**0.001**
Total lean mass	0.99 (0.91-1.08)	0.81
Total Fat mass	1.01 (0.96-1.07)	0.72
Vitamin C	0.98 (0.91-1.05)	0.57
Vitamin E	0.90 (0.78-1.05)	0.18

*P value is adjusted for age and surgery type, except gastric bypass (only adjusted for age) and age (only adjusted for surgery type). To perform this analysis, patients with osteopenia at baseline were excluded. Corrected Ca albumin-corrected plasmatic calcium, P+ phosphorus, Mg magnesium, PTH parathyroid hormone, CTX s-carboxy-terminal cross-linked telopeptide type 1 collagen, BMD bone mineral density, BMC bone mineral content

Supplementary table E: Missing information

Variable	Baseline	6 months	12 months	24 months
Demographic data and Comorbidities				
Age	0	-	-	-
Menopause	0	-	-	-
DM2	3	-	2	25
HT	32	-	56	86
Dyslipidemia	4	-	6	24
Osteopenia	0	-	7	32
Sarcopenic Obesity	9	-	9	36
Anthropometric data				
Weight (kg)	2	2	2	24
BMI (kg/m^2)	2	2	2	24
SBP (mmHg)	67	114	113	126
DBP (mmHg)	68	114	113	126
Body composition				
BMC (g)	0	-	7	32
Body fat mass (kg)	0	-	7	32
Total body fat (%)	0	-	7	32
Trunk fat (%)	0	-	7	32
Legs fat (%)	0	-	7	32
Total lean mass (kg)	0	-	7	32

Arms lean mass (kg)	0	-	7	32
Legs lean mass (kg)	0	-	7	32
L1-L4 BMD (g/cm^2)	0	-	7	32
L1-L4 T-score	0	-	7	32
L1-L4 Z-score	0	-	7	32
Femoral neck BMD (g/cm^2)	0	-	7	32
Femoral neck T-score	0	-	7	32
Femoral neck Z-score	0	-	7	32
Total femur BMD (g/cm^2)	0	-	7	32
Total femur T-score	0	-	7	32
Total femur Z-score	0	-	7	32
Total body BMD (g/cm^2)	0	-	7	32
Total body T-score	0	-	7	32
Total body Z-score	0	-	7	32
FRAX® major	2	-	8	36
FRAX® hip	2	-	8	36
Laboratory Parameters				
25-OH-Vitamin D (ng/mL)	4	7	6	25
P+ (mg/dL)	5	7	5	25
Mg (mEq/L)	8	10	8	27
Corrected Ca (mg/dL)	4	8	6	26
PTH (pg/mL)	7	9	7	28
Osteocalcin (ng/mL)	18	25	22	51
CTX (µg/L)	16	24	20	50
24h urine calcium (mEq/24h)	38	39	11	53
STP (g/L)	9	11	9	29
HbA1c (%)	4	13	6	26
LDL (mg/dL)	4	6	4	26
TG (mg/dL)	4	6	4	25
GGT (U/L)	7	9	7	28
ALP (U/L)	5	7	5	26
AST (U/L)	8	10	8	29
ALT (U/L)	4	6	4	25
eGFR (mL/min/1.73m^2)	3	5	3	24
Microalbuminuria (mg/L)	6	16	12	30
Iron (µg/dL)	9	11	9	29
Transferrin (mg/dL)	9	11	9	29
Ferritin (ng/mL)	9	11	9	29
Folic acid (ng/mL)	12	14	12	32
Vitamin B12 (pg/mL)	8	10	8	29
TSH (µUI/mL)	5	7	5	25
Total bile acids (µmol/L)	12	-	12	30
Vit E (µg/mL)	13	-	14	39
Vit C (µg/mL)	12	-	13	39

Abbreviations: *BMI* body mass index, *RYGB* roux-en-Y gastric bypass, *SG* vertical sleeve gastrectomy, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *DM2* type 2 diabetes, *HT* hypertension, *BMC* bone mineral content, *L1-L4* lumbar spine from 1 to 4, *BMD* bone mineral density. STP serum total protein, FG fasting glucose, HbA1c hemoglobin A1c, CT total cholesterol, HDL high-density lipoprotein cholesterol, LDL low-density lipoprotein cholesterol, TG triglycerides, GGT gamma-glutamyltransferase, ALP alkaline phosphatase, AST aspartate aminotransferase, ALT alanine aminotransferase, eGFR estimated glomerular filtration rate, P+ phosphorus, Corrected Ca albumin-corrected plasmatic calcium, Mg magnesium, PTH parathyroid hormone, CTX s-carboxy-terminal cross-linked telopeptide type 1 collagen, T4L free thyroxine, TSH thyroid-stimulating hormone. *Vit D insufficiency refers to the prevalence of this condition in the presented timepoint and not to a variation.

Evaluating the Roles of FGF-21 and FGF-23 in Bone Metabolism After Bariatric Surgery: Reminiscences from the BARIATRIC BONE Study (data not published)

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Affiliations described in detail on page 73 of this thesis.

1. Introduction

As mentioned previously in the BARIATRIC BONE study, bariatric surgery (BS) is associated with marked bone mineral density reductions that are more pronounced after Roux-en-Y gastric bypass, affecting mostly the hip but also the lumbar spine[31]. The mechanisms traditionally related with bone loss in this context include mechanical unloading, nutritional deficiencies and inadequate supplementation of vitamin D or calcium (with associated secondary hyperparathyroidism) and changes in the production of adipocyte or gut-derived hormones[32].

In recent years, uncharted players of bone metabolism following metabolic surgery, such as Fibroblast growth factor 21 (FGF-21) and Fibroblast growth factor 23 (FGF-23), have gained increased interest [33, 34]. FGF-21, a hormone produced mainly in the liver and adipose tissue, is known to have a regulatory role in carbohydrate and lipidic metabolism. Most of the evidence available to date has also shown that FGF21 seems to have globally deleterious effects on bone[35]. However, documentation establishing a link between FGF21 and bone homeostasis is still limited, and no papers to date addressed this issue in a bariatric context.

On other hand, bone acts as an endocrine organ by producing FGF-23 through its osteocytes and osteoblasts. This hormone inhibits the proximal tubular resorption of phosphate and leads to a decrease in active vitamin D levels, which globally contributes to a decrease in serum phosphate levels[36]. Growing clinical data supports an association between FGF-23 levels, abnormal bone homeostasis and fragility fractures (mainly in the elderly and in chronic kidney disease)[37]. Despite this fact, its role after bariatric surgery is scarcely documented.

Therefore, we aim to investigate whether variations of FGF-21 and FGF-23 levels one and two years after metabolic surgery are associated with BMD variation after these procedures.

2. Methods

The adopted methodologies were already described previously in the BARIATRIC BONE study. In this analysis, we focused on the FGF-21 and FGF-23 levels, that were evaluated after the publication of the main paper. The authors used the blood samples of the included patients collected before, one and two years after bariatric surgery. These samples were analyzed with Human FGF-23 and FGF-21 ELISA Kits (Thermofisher Scientific®). The limit of detection (LOD) for the FGF-23 kit was 71.8pg/mL and for the FGF-21 kit was 31.2pg/mL. For the three patients with results of FGF2-23 below the LOD, a value of LOD/2 was considered.

3. Results

We collected data regarding FGF levels for 116 patients (36 submitted to SG and 80 to RYGB) (Table 3 cont.). Most patients presented FGF-21 levels below the LOD before surgery (70.7%), but with a substantially greater proportion of these cases among patients submitted to SG (91.7 vs 61.2%, p=0.001). The variation of FGF-21 levels after surgery was also undetectable mostly in SG group, with this happening in 88.9 *vs* 55% (p=0.001) one year and 88.9 vs 62.5% (p=0.01) two years after surgery. Before RYGB, 31 patients presented detectable FGF-21 levels, with a median of 104.7pg/mL at baseline. Among these patients with detectable values before RYGB, FGF-21 levels suffered a slight increase one (+25.3pg/mL) and two years (+22.3pg/mL) after the procedure. Regarding FGF-23, its levels at baseline were higher among patients awaiting SG (534.5 *vs* 335.6pg/mL, p=0.003). Although RYGB induced greater positive variations of FGF-23 levels one (+116.7 vs +32.7pg/mL) and two years (+164.4 vs +93.8pg/mL) after surgery, there were no statistically significant differences between surgical techniques. FGF-21 and FGF-23 were not predictors of BMD variation in total femur, femoral neck and lumbar spine two years after surgery (Table 4 cont.). Despite this fact, there was a

trend for baseline FGF-23 levels to predict osteopenia/osteoporosis 2 years after BS [OR 3.50 (0.88-13.96), p=0.075] [Supplementary table D (cont.)].

Table 3 (cont.) Comparative analysis of laboratory parameters at baseline, and their variation one and two years after BS (n=116)

	Baseline				**Variation one year after BS**				**Variation two years after BS**			
Variable	Overall sample (n=116)	SG (n=36)	RYGB (n=80)	*P* value	SG (n=36)	RYGB (n=80)	*P* value	*P* adj.*	SG (n=36)	RYGB (n=80)	*P* value	*P* adj.*
FGF21				**0.001**			**<0.001**	**0.001**			**0.004**	**0.010**
Undetected	92 (70.7)	33 (91.7)	49 (61.2)		32 (88.9)	44 (55.0)			32 (88.9)	50 (62.5)		
Detected	34 (29.3)	3 (8.3)	31 (38.8)		4 (11.1)	36 (45.0)			4 (11.1)	30 (37.5)		
FGF21 (pg/mL), median [min-max]	109.1 [44.2, 2225.9]	325.2 [61.5, 2225.9]	104.7 [44.2, 297.4]	0.261	-113.4 [-563.2, -11.8]	25.3 [-201.5, 2005.9]	**0.030**	**<0.001**	-28.9 [-1572.5, 6.3]	22.3 [-178.0, 1259.5]	0.185	0.516
FGF23 (pg/mL), median [min-max]	378.0 [35.9, 16436.5]	534.5 [190.1, 16436.5]	335.6 [35.9, 119000.0]	**0.003**	32.7 [-4527.5, 11321.3]	116.7 [-2632.4, 12564.7]	0.171	0.561	93.8 [-3768.3, 11441.6]	164.4 [-3334.0, 15209.2]	0.725	0.752

**P* adj. is adjusted for age and weight variation (the same happening with Table 3 of the BARIATRIC BONE study)

Table 4 (cont.) Linear regression analysis with the baseline predictors of BMD variation in different bone areas 2 years after surgery (n=110)

	BMD variation – total femur		BMD variation – femoral neck		BMD variation – lumbar spine	
Baseline predictors	β (95%CI)	*P value**	β (95%CI)	*P value**	β (95%CI)	*P value**
FGF21 detected	0.18 (-0.02 to 0.05)	0.346	0.03 (-0.00 to 0.07)	0.077	0.02 (-0.02 to 0.06)	0.225
FGF21 (*per* 10000 pg/mL)	0.34 (-0.40 to 1.07)	0.362	-0.14 (-0.85 to 0.58)	0.708	-0.09 (-0.87 to 0.69)	0.821
FGF23 (*per* 10000 pg/mL)	0.00 (-0.04 to 0.05)	0.896	-0.01 (-0.05 to 0.04)	0.723	0.02 (-0.02 to 0.07)	0.316

**P value* is adjusted for age and surgery type.

Supplementary table D (cont.) Logistic regression analysis with the baseline predictors of osteopenia/osteoporosis 2 years after surgery (n=110)

	Osteopenia or osteoporosis	
Baseline predictors	OR (95%CI)	*P value**
FGF21 detected	1.27 (0.43-3.75)	0.659
FGF21 (*per* 10000 pg/mL)	0.08 (0.05-1.21)	0.847
FGF23 (*per* 10000 pg/mL)	3.50 (0.88-13.96)	0.075

**P value* is adjusted for age and surgery type

4. Discussion

In this study, we shed some light on the variation of FGF-23 and 21 levels according to surgery type and their putative roles in BMD variation.

We found that there were no differences in FGF-23 variation between groups although patients submitted to SG presented higher FGF-23 levels at baseline. A case-control study performed in 20 women before bariatric surgery (matched with 20 controls for race and age) showed that fibroblast FGF23 levels were higher in surgical group (42.4 *vs* 25.9pg/mL). Remarkably, leptin independently predicted FGF-23 levels in these patients, raising the possibility of a paracrine or endocrine effect affecting FGF-23 production in bone[38]. One cross-sectional study showed no differences in serum FGF-23 levels post-gastric bypass/ biliopancreatic diversion with duodenal switch when compared with controls with class II and III obesity (but no FGF-23 data pre-surgery was presented, neither the 1-25 dihydroxyvitamin D levels)[39]. Another article included 22 adults with obesity and type 2 diabetes (59% male) submitted to sleeve gastrectomy (SG). It was found that FGF23 concentrations measured a year after surgery decline in this setting of significant weight loss (-12.4pg/mL, 95% CI: -19.5 to 2.0, P = 0.005), suggesting that high levels of FGF-23 may be a downstream result of obesity[33] (an idea also shared by other authors[40]). Interestingly, our study showed an increase in its levels at one and two years after surgery. There is evidence that deleting *Fgf23 gene* from mice adipocytes protects from diet-induced weight gain and metabolic imbalances, such as hyperglycemia and dyslipidemia, while preventing lean mass wasting[41]. Thus, it could be hypothesized that this elevation in FGF-23 levels after surgery (more pronounced after RYGB) may be linked to muscle mass loss and, indirectly, to potential bone mass loss.

Regarding FGF-21 levels, our study showed a greater proportion of patients submitted to SG with undetectable levels at baseline, a pattern that consistently extended to its postoperative variation, suggesting lower levels of this hormone in this group. Considering that circulating FGF21 levels are increased in states of worse metabolic dysfunction (being often related with diabetes and fatty liver disease)[42], is not surprising that the group submitted to SG presented

lower FGF 21 values, being compatible with a metabolically less stressed subgroup. A study by Crujeiras AB et al. showed that FGF-21 levels were increased after bariatric surgery (especially 1 month after BS) while the opposite occurred after energy-restricted treatments, a fact that was independent of the weight reduction magnitude, insulin sensitivity or ketosis (positioning FGF-21 as a putative marker of severe nutritional stress)[43]. A meta-analysis from 2020 found that RYGB is significantly associated with augmented FGF-21 and that, in studies with longer follow-up (≥ 1 year), FGF-21 levels decreased significantly following BS[44]. In a rat sleeve gastrectomy model, serum FGF-21 levels increased after surgery, being in line with some human studies[45]. Previous data supported the idea that genetic and pharmacologic FGF-21 gain of function contributed to decreased bone mass (seemingly through osteoblastogenesis inhibition), while FGF-21 loss of function could lead to a reciprocal high-bone-mass phenotype[46, 47]. Despite this fact, other studies conducted in mice and monkeys disputed this notion exhibiting no relevant changes in bone mineral density/content[48].

This paper presents the first study to date addressing the possible implications of FGF-23 and FGF21 in bone metabolism after bariatric surgery. It is also the first to our knowledge regarding FGF-23 levels specifically after gastric bypass, following a prospective two-year cohort design.

Conclusions

FGF-21 and FGF23 did not predict BMD variations in lumbar spine, total femur and femoral neck after bariatric surgery. No statistically significant differences were seen globally between surgical techniques in the variation of these two hormones.

Article 2

Secondary Hyperparathyroidism Among Bariatric Patients: Unraveling the Prevalence of an Overlooked Foe.

Mendonça FM, Neves JS, Silva MM, Borges-Canha M, Costa C, Cabral PM, Guerreiro V, Lourenço R, Meira P, Ferreira MJ, Salazar D, Pedro J, Viana S, Souto S, Varela A, Belo S, Lau E, Freitas P, Carvalho D; CRIO

Obesity surgery journal

Published in 2021

Obesity Surgery (2021) 31:3768–3775
https://doi.org/10.1007/s11695-021-05495-7

ORIGINAL CONTRIBUTIONS

Secondary Hyperparathyroidism Among Bariatric Patients: Unraveling the Prevalence of an Overlooked Foe

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Received: 20 August 2020 / Revised: 20 May 2021 / Accepted: 20 May 2021 / Published online: 12 June 2021
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Abstract

Introduction Bariatric surgery (BS) is the most effective therapeutic approach to obesity. It is associated with great gastrointestinal anatomic changes, predisposing the patients to altered nutrient absorption that impacts phosphocalcium metabolism. This study aimed to clarify the prevalence of secondary hyperparathyroidism (SHPT) and its predictors in patients submitted to BS.

Methods Retrospective study of 1431 patients who underwent metabolic surgery between January 2010 and June 2017 and who were followed for at least 1 year. We compared the clinical and biochemical characteristics of patients with and without secondary hyperparathyroidism (considering SHPT a PTH > 69 pg/mL). Two different analyses were performed: (1) paired analysis of participants before and 1 year after surgery (N = 441); (2) Cross sectional analysis of participants submitted to bariatric surgery before (N = 441), 1 year after (N = 1431) and 4 years after surgery (N = 333). Multiple logistic regression models were used to evaluate possible predictors of SHPT after BS.

Results The overall prevalence of SHPT was 24.9% before surgery, 11.2% 1 year after surgery and 21.3% 4 years after surgery. Patients submitted to LAGB had the highest prevalence of SHPT 1 year after surgery (19.4%; vs RYGB, 12.8%, vs SG, 5.3%). Four years after surgery, RYGB had the highest prevalence of SHPT (27.0%), followed by LAGB (13.2%) and SG (6.9%). Higher body mass index and age, decreased levels of vitamin D and RYGB seem to be independent predictors of SHPT 1 year after surgery. The only independent predictor of SHPT 4 years after surgery was RYGB.

Conclusion The prevalence of SHPT is higher before and 4 years after BS than 1 year after surgery. This fact raises some questions about the efficacy of the implemented follow-up plans of vitamin D supplementation on the long term, mainly among patients submitted to RYGB.

Keywords Bariatric surgery · Secondary Hyperparathyroidism · Calcium · Vitamin D · Supplementation

Key Points
Bariatric surgery is associated with secondary hyperparathyroidism (SHPT).
Prevalence of SHPT is higher before and 4 years after bariatric surgery than 1 year after surgery.
Efficacy of the implemented follow-up plans of vitamin D supplementation should be revised.

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Introduction

Obesity is a major health problem worldwide, being defined as body mass index (BMI) ≥ 30 kg/m^2. This chronic disease has been steadily increasing during the last 5 decades, reaching pandemic proportions nowadays [1]. In Portugal, 18 to 21% of the population will be affected by this condition if no action is taken [2]. This becomes even more serious when considering that obesity is associated with several other disturbances, such as cardiovascular diseases, hypertension, obstructive sleep apnea, depression, dyslipidemia, and cancer, in addition to decreased quality of life and increased all-cause mortality [1, 3]. The efficacy shown by bariatric surgery (BS) to tackle this problem and its related comorbidities, led to a significant increase in the popularity of this therapeutic approach [4]. Despite its multiple benefits, BS has obvious downsides. For instance, it may predispose to increased incidence of bone fractures [5, 6]. The issue is controversial [6] and may result from phosphocalcium disturbances, namely hyperparathyroidism secondary to nutritional (calcium and vitamin D) deficiencies. Considering that secondary hyperparathyroidism (SHPT) may be related with several diseases (such as hypertension) [7], it became important to address this issue among patients submitted to bariatric surgery.

We aimed (1) to study the prevalence of SHPT before and 1 year after bariatric surgery, taking into account the type of surgery performed, (2) to clarify the differences between surgical patients with obesity that have SHPT and those without that pathology, and (3) to find the predictors of SHPT 1 year and 4 years after bariatric surgery.

Methods

Retrospective unicentric study of the prevalence of SHPT among bariatric patients with obesity submitted to bariatric surgery consecutively selected between January 2010 and June 2017. The included patients were followed by the Integrated Responsibility Center for Obesity (CRIO group) and all of them met the following eligibility criteria:

- Body mass index (BMI) ≥ 35 kg/m^2 with two or more preoperative comorbidities (diabetes mellitus type 2, dyslipidemia, hypertension, obstructive sleep apnea syndrome, among others) or BMI ≥ 40 kg/m^2;
- Adult patients with no more than 65 years;
- Non-satisfactory weight loss after, at least, a year under all the appropriate non-surgical measures;
- Obesity non-secondary to classical endocrine disease;
- Understanding of the surgical procedure and adherence to a long-term follow-up plan;
- Absence of non-stabilized psychiatric disturbances or alcohol/narcotic abuse.
- Follow-up for, at least, 12 months after surgery.

Two different analyses were performed: (1) paired analysis of participants before and 1 year after surgery (N = 441); (2) cross-sectional analysis of participants submitted to BS before (N = 441), 1 year after (N = 1431) and 4 years after surgery (N = 333). For the paired analysis, we included participants with PTH before and 1 year after surgery. For the cross-sectional analysis, we included participants with PTH evaluation available at each timepoint. In the paired analysis, we divided the patients in three groups considering the type of surgery performed [sleeve gastrectomy (SG), laparoscopic adjustable gastric banding (LAGB) or Roux-en-Y gastric bypass (RYGB)] and evaluated multiple parameters related with phosphocalcium metabolism [total serum calcium (Ca), magnesium(Mg2+), phosphorus (P+), Parathormone (PTH), 25-OH vitamin D (VitD), alkaline phosphatase (ALK-P), and proportion of supplemented VitD patients]. The proportion of patients taking supplements was calculated based on medical reporting on clinical files.

Vitamin D deficiency was assumed when serum levels were < 30 ng/mL. We compared these parameters between baseline and 12 months after surgery to understand how different bariatric surgery techniques impact on the presented surrogates of bone metabolism.

On the cross-sectional analysis, participants in each timepoint were divided in two groups: those with secondary hyperparathyroidism (SHPT) vs without SHPT, assuming this entity if PTH > 69 pg/mL (based on the cutoff adopted in our institution). To understand the characteristics of patients with and without high PTH levels before and after bariatric surgery, these groups were compared before surgery, at 12 months and at 48 months after the procedure. This comparison addressed various important aspects such as sex, body mass index (BMI), and percentage of weight loss, blood pressure, glucose and phosphocalcium metabolism parameters, Ca and VitD supplementation, and the proportion of surgery techniques among these groups. Finally, we investigated the predictors of SHPT 12 and 48 months after bariatric surgery.

In addition to the specific supplements presented in this article (25-OH vitamin D, Ca), multivitamin supplements were prescribed to every patient submitted to bariatric surgery (as a routine procedure). The supplements of VitD used were either cholecalciferol pills (between 22,400 and 30,000 international units each) or cholecalciferol oral solution (0.5 mg/ml, 667 international units per droplet) that were prescribed in different supplementation schemes according to the degree of VitD deficiency present in the post-operative periodic serum 25-OH vitamin D measurements (at least 3000 IU/day and as high as 6000 IU/day, independently of the surgery technique). Values of 25-OH vitamin under 10 pg/mL were treated with 5000–6000 IU/day, values between 10 and 20 pg/mL with 4000–5000 IU/day and values between 20 and 30 pg/mL with 3000–4000 IU/day. These doses were latter adjusted taking into account the following measurements of serum 25-OH vitamin D.

In the unusual cases of calcium deficiency (Ca < 4.3 mEq/L), patients were prescribed with calcium carbonate tablets (between 1000 and 1500 mg per tablet, taken with meals) to correct existent deficits. We only supplemented with calcium carbonate tablets because calcium citrate is still not available in our country. It is relevant to mention that the protocol of our hospital regarding the analytical studies performed on bariatric patients changed in 2015 and, for this reason, we only started to have baseline data regarding phosphocalcium metabolism after this year.

Blood pressure measurements were made during endocrinology consultations (included in the follow-up protocol of bariatric patients) with the patient comfortably seated for at least 5 minutes.

Serum levels of PTH were assessed through in vitro chemiluminescent microparticle immunoassay (ARCHITECT ci4100 Integrated System, Abbott Diagnostics Laboratories, Abbott Park, IL 60064, USA, Abbott 65205, Wiesbaden, Germany).

This study was approved by the ethics committee for health of our hospital.

Statistical Analysis

Paired analysis was performed with paired t test and McNemar's test. Cross-sectional analysis was performed with chi-square test and one-way ANOVA. In order to analyze the predictors of SHPT 12 and 48 months after surgery, a logistic regression was performed, adjusted to following variables (age, sex, BMI, RYGB, 25-OH VitD, Ca, P+, ALK-P).

Continuous variables with normal distribution were presented as means and standard deviations. Continuous variables with non-normal distribution were described as medians and interquartile range. Categorical variables were expressed as percentages. Reported p values are two-tailed and $p \leq 0.05$ was considered statistically significant. Analyses were performed with the use of SPSS Statistics 26® software.

Results

Among the 1431 patients included in this study, 1248 (87.2%) were female and 183 were male (12.8%) individuals, with a mean age of 42.6 years old and mean BMI of 43.6 kg/m^2. The majority of patients underwent RYGB (58%), 29.1% underwent SG (n = 416) and 12.9% (n = 185) LAGB.

The Impact of Surgery Technique (Paired Analysis)

Regarding the proportion of SHPT in the group of patients with baseline data (n = 441), it was 24.9% at baseline and 11.1% 1 year after surgery (Table 1). These proportions were higher at baseline in every surgery type, mirroring the lower PTH levels 1 year after surgery. The percentage of patients with SHPT at 1 year was higher among those submitted to LAGB (19.4%) and lower among those submitted to SG (5.8%). Higher 25-OH VitD levels were seen 1 year after surgery, independently of the surgical procedure, the same happening with the proportion of 25-OH VitD supplemented patients (that was higher in those submitted to SG–25.2%, followed by those submitted to RYGB–20.7%). Despite the apparent increase in the supplementation rates, no surgical group attained mean 25-OH VitD levels ≥ 30 ng/mL 1 year after surgery. Ca levels were also higher after surgery in every types of surgery. In turn, ALK-P levels increased after surgery in the case of RYGB (81.4 to 85.8 mg/dL) and decreased after LAGB (76.9 to 68.8 mg/dL). There was also a slight decrease in ALK among those patients submitted to SG (76.0 to 74.9 mg/dL). Magnesium levels remained stable after surgery, with no significant variation between procedures (Table 2).

Differences Between Participants According to SHPT Status (Cross-Sectional Analysis)

When we divided the patients in two groups, considering the diagnosis of SHPT, we found that there were no differences at baseline (Table 3) regarding age, systolic, or diastolic blood pressure, glycemic status, ALK-P or CRP. The proportion of female patients was higher among those with SHPT (88.2 vs 86.1%, p < 0.001), the same happening with BMI (44.6 vs 43.1 kg/m^2, p = 0.015). The results in patients with SHPT also revealed significantly lower baseline levels of Ca (4.60 vs 4.70 mEq/L, p < 0.001) and 25-OH VitD (13.1 vs 15.9 ng/mL, p < 0.001), a fact also observed with P+ levels (3.25 vs 3.38 mg/dL, p = 0.013). Conversely, Mg2+ levels among these patients were higher (1.61 vs 1.57 mEq/L, p = 0.007), the same happening with the proportion of subjects supplemented with Ca (0.9 vs 0.3%, p < 0.001) and 25-OH VitD (13.8 vs 6.7%, p < 0.001). Despite this fact, the proportion of 25-OH VitD deficiency was also increased at baseline in the group with SHPT.

When we focused on the timepoint of 1 year after surgery, patients with SHPT were older (45.6 vs 42.1 years, p < 0.001), with higher BMI (32.1 vs 30.0 kg/m^2, p < 0.001) and lower percentage of weight lost (27.7 vs 31.1%, p < 0.001). In addition, they presented with higher SBP (126.8 vs 121.7 mmHg, p < 0.001) and DBP (77.9 vs 74.9 mmHg, p < 0.001), the same happening with plasmatic glucose (90.4 vs 85.3 mg/dL, p < 0.001) and HbA1c (5.5 vs 5.3%, p < 0.001). ALK-P levels were also increased in these subjects 1 year after surgery (90.0 vs 79.5, p < 0.001). On the other hand, 25-OH VitD levels were lower among subjects with SHPT (19.9 vs 24.2 ng/mL, p < 0.001). Despite the higher rates of 25-OH VitD supplementation in that group (26.4 vs 19.3%, p = 0.043), most patients with SHPT at 1 year had also 25-OH VitD deficiency (57.2 vs 36.7%, p < 0.001). No differences

Table 1 Paired analysis of participants before and 1 year after surgery (N = 441)

Parameter evaluated	Before surgery	1 year after surgery	P value	Reference values
Age (years)–baseline	42.6 ± 10.7	–	–	
Female (%)	87.2	–	–	
Surgery type (n, % of total)				
Laparoscopic adjustable gastric banding	36 (8.2%)	–	–	
Sleeve gastrectomy	131 (29.7%)			
Gastric bypass	274 (62.1%)			
BMI (kg/m^2)	43.5 ± 5.6	29.9 ± 5.3	< 0.001	17.5–24.9
Creatinine (mg/dL)	0.70 ± 0.22	0.64 ± 0.19	< 0.001	0.51–0.95
Ca (mEq/L)	4.67 ± 0.22	4.75 ± 0.19	< 0.001	4.3–5.3
Mg2+ (mEq/L)	1.58 ± 0.17	1.63 ± 0.13	< 0.001	1.55–2.05
Phosp (mg/dL)	3.34 ± 0.58	3.66 ± 0.49	< 0.001	2.7–4.5
PTH (pg/mL)	59.0 ± 25.0	50.2 ± 47.1	< 0.001	10–69
SHPT (%)	24.9%	11.1%	< 0.001	--------
25-OH VitD (ng/mL)	15.2 ± 8.4	25.0 ± 10.8	< 0.001	> 30
25-OH VitD deficiency (%)	72.8%	33.8%	< 0.001	–
Vit D supplementation–baseline (%)	8.4%	21.6%	< 0.001	–
ALK-P (mg/dL)	80.7 ± 26.4	81.0 ± 23.6	0.784	30–120

BMI body mass index, *Ca* total plasmatic calcium, *P*+ phosphorus, *Mg* magnesium, *PTH* parathormone, *SHPT* secondary hyperparathyroidism, *25-OH VitD* 25-hidroxivitamin D, *ALK-P* total alkaline phosphatase, *CRP* C-reactive protein

between groups were found regarding Ca levels. Only 6 patients were supplemented with calcium carbonate 1 year after surgery, all without SHPT. In the last timepoint (4 years after surgery), the only variables that showed statistically significant differences between those two groups were the proportion of 25-OH VitD supplementation (26.4 vs 19.3%, p = 0.043) and ALK-P levels (94.6 vs 78.3 mg/dL, p < 0.001) both higher among patients with SHPT (Table 4).

Table 2 Clinical and analytical characteristics of the subgroup of patients (N = 441) that present data at baseline and 1 year after surgery (considering surgery type)

	Laparoscopic adjustable gastric banding (N = 36; 8.2%)		P value	Sleeve gastrectomy (N = 131; 29.7%)		P value	Roux-en-Y gastric bypass (N = 274; 62.1%)		P value
	Baseline	1 year		Baseline	1 year		Baseline	1 year	
Age (years)	40.5 ± 14.0	–		42.0 ± 18.0	–		41.0 ± 15.0	–	
Female (%)	83.3%	–		80.9%	–		89.8%	–	
BMI (kg/m^2)	41.7 ± 3.6	35.6 ± 3.9	< 0.001	43.9 ± 6.6	30.8 ± 6.3	< 0.001	43.3 ± 6.3	28.8 ± 4.4	< 0.001
Ca (mEq/L)	4.68 ± 0.18	4.78 ± 0.18	0.012	4.66 ± 0.20	4.77 ± 0.18	< 0.001	4.68 ± 0.23	4.74 ± 0.20	< 0.001
Mg2+ (mEq/L)	1.55 ± 0.18	1.54 ± 0.15	0.666	1.57 ± 0.18	1.64 ± 0.15	0.040	1.58 ± 0.13	1.64 ± 0.12	< 0.001
P+ (mg/dL)	3.43 ± 0.46	3.40 ± 0.48	0.799	3.37 ± 0.46	3.57 ± 0.44	< 0.001	3.33 ± 0.61	3.74 ± 0.50	< 0.001
PTH (pg/mL)	57.5 ± 24.3	54.6 ± 26.1	0.367	59.8 ± 27.5	40.6 ± 20.7	< 0.001	58.5 ± 23.9	44.8 ± 23.2	0.011
SHPT (%)	25.0	19.4	0.571	23.7	5.3	< 0.001	25.5	12.8	< 0.001
25-OH VitD (ng/mL)	11.7 ± 6.3	21.0 ± 10.6	< 0.001	16.0 ± 8.3	28.2 ± 11.4	< 0.001	15.2 ± 8.4	23.5 ± 10.1	< 0.001
25-OH VitD deficiency (%)	75.0	63.9	0.007	83.2	51.9	< 0.001	85.5	69.7	< 0.001
Vit D supplementation (%)	11.1	15.6	0.584	11.5	25.2	0.005	6.6	20.7	< 0.001
ALK-P (mg/dL)	76.9 ± 20.1	68.8 ± 16.3	0.002	76.0 ± 30.0	74.9 ± 23.4	0.021	81.4 ± 24.5	85.8 ± 22.9	0.006

BMI body mass index, *Ca* total plasmatic calcium, *P*+ phosphorus, *Mg* magnesium, *PTH* parathormone, *SHPT* secondary hyperparathyroidism, *25-OH VitD* 25-hidroxivitamin D, *ALK-P* total alkaline phosphatase, *CRP* C-reactive protein

Table 3 Comparison between patients with or without SHPT 1 year and 4 years after surgery (N = 1431)

	1 year after surgery			4 years after surgery		
	No SHPT N = 1271 (88.8%)	SHPT N = 160 (11.2%)	P value	No SHPT N = 262 (78.7%)	SHPT N = 71 (21.3%)	P value
Age (years)	42.1 ± 10.6	45.6 ± 10.2	< 0.001	43.0 ± 10.1	44.2 ± 10.5	0.40
Female (%)	87.2	87.5	0.91	90.8	85.9	0.22
BMI (kg/m^2)	30.0 ± 5.2	32.1 ± 5.8	< 0.001	31.6 ± 5.6	31.9 ± 6.0	0.75
Weight lost (%)	31.1 ± 10.1	27.7 ± 11.4	< 0.001	27.8 ± 11.1	27.5 ± 10.5	0.82
Waist circumference (cm)	93.9 ± 13.6	99.3 ± 12.0	0.001	97.8 ± 15.5	100.4 ± 15.9	0.43
SBP (mmHg)	121.7 ± 10.7	126.8 ± 16.8	0.002	122.4 ± 15.9	124.7 ± 18.8	0.51
DBP (mmHg)	74.9 ± 10.7	77.9 ± 10.6	0.006	73.4 ± 10.1	75.9 ± 10.6	0.24
Fasting glucose (mg/dL)	85.3 ± 13.0	90.4 ± 25.4	< 0.001	89.3 ± 20.9	88.8 ± 15.0	0.86
HbA1c (%)	5.3 ± 0.5	5.5 ± 0.8	< 0.001	5.5 ± 0.7	5.5 ± 0.5	0.96
Ca (mEq/L)	4.8 ± 0.2	4.8 ± 0.2	0.89	4.6 ± 0.2	4.6 ± 0.2	0.85
PTH (pg/mL)	42.5 ± 12.1	79.1 ± 23.1	< 0.001	46.1 ± 12.2	83.4 ± 32.2	< 0.001
25-OH VitD (ng/mL)	24.2 ± 13.0	19.9 ± 10.8	< 0.001	22.4 ± 8.9	25.3 ± 35.6	0.25
P+(mg/dL)	3.7 ± 0.5	3.6 ± 0.5	0.038	3.5 ± 0.5	3.4 ± 0.6	0.52
Mg (mEq/L)	1.6 ± 0.1	1.6 ± 0.1	0.13	1.6 ± 0.1	1.7 ± 0.1	0.24
25-OH VitD deficiency (%)	36.7%	57.2%	< 0.001	41.5%	47.8%	0.36
Vit supplem. (%)	19.3	26.4	0.043	25	45.2	0.002
Ca supplem. (%)	0.5	0.0	0.89	0.0	0.0	–
ALK-P (mg/dL)	79.5 ± 24.6	90.0 ± 28.3	< 0.001	78.3 ± 25.2	94.6 ± 27.2	< 0.001
CRP (mg/L)	3.9 ± 8.9	3.8 ± 8.2	0.67	4.9 ± 20.6	2.1 ± 2.2	0.044
Surgery type:						
Adjustable gastric banding(%)	88.1	11.9	–	86.8	13.2	–
Sleeve gastrectomy(%)	94.0	6.0	–	93.1	6.9	–
Roux-en-Y gastric bypass (%)	86.4	13.6	–	73.0	27.9	–

SHPT secondary hyperparathyroidism, *BMI* body mass index, *Ca* total plasmatic calcium, *P+* phosphorus, *Mg* magnesium, *ALK-P* total alkaline phosphatase, *CRP* C-reactive protein

When we studied the predictors of SHPT 1 year after surgery, we found that older age, higher BMI, lower 25 OH-VitD levels, and RYGB surgery were associated with SHPT. On the other hand, the predictors of SHPT 4 years after surgery were RYGB surgery and higher ALK-P levels (Table 4).

Discussion

The presented results demonstrate that the prevalence of SHPT is high among bariatric patients even before surgery, a fact that is in line with other published data [8]. One possible

Table 4 Multivariate logistic regression analysis with the predictors of SHPT 1 and 4 years after surgery

	1 year after surgery		4 years after surgery	
Variable	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.033 (1.014–1.053)	0.001	1.005 (0.973–1.037)	0.764
Sex	1.392 (0.734–2.642)	0.312	0.826 (0.301–2.267)	0.711
BMI	1.068 (1.028–1.109)	0.001	1.042 (0.984–1.103)	0.161
RYGB	2.663 (1.549–4.577)	< 0.001	9.809 (2.157–44.602)	0.003
25-OH VitD	0.975 (0.956–0.994)	0.013	1.005 (0.970–1.042)	0.769
Ca	1.550 (0.622–3.867)	0.347	1.364 (0.225–8.278)	0.736
P+	0.716 (0.475–1.079)	0.110	0.748 (0.387–1.444)	0.387
ALK-P	1.006 (0.998–1.013)	0.150	1.021 (1.008–1.034)	0.001

OR adjusted odds ratio, *BMI* body mass index, *P+* phosphorus, *RYGB* Roux-en-Y gastric bypass, *25-OH VitD* 25-hidroxivitamin D, *Ca* total plasmatic calcium, *ALK-P* alkaline phosphatase

explanation is the low 25-OH VitD levels and consequent higher proportion of 25-OH VitD deficiency among these patients with obesity. Individuals with obesity may be predisposed to become 25-OH VitD deficient due to its sequestration or volumetric dilution in increased body fat stores, inadequate intake of supplements, and foods containing this hormone and also due to reduced sunlight exposure [9, 10]. Other putative contributor are the slightly lower Ca levels that, even in the normal range, may lead to increased PTH production, a mechanism regarded in several sources [11, 12]. Considering this, an aggressive approach regarding 25-OH VitD supplementation before bariatric surgery may be recommended [13].

Surprisingly, the proportion of baseline SHPT in this study was even higher than 1 year or 4 years after surgery, a fact that leads to hypothesize [12] that obese state may contribute to SHPT. The increased proportion of SHPT before surgery in our study may also be explained, at least in part, by the higher 25-OH VitD supplementation rates after surgery, that seemed to conduct to an increase in vitamin D levels and diminished percentage of 25-OH VitD deficiency at 1 year after surgery. These results are in line with recent data, that show an initial decline and then a progressive increase in PTH levels and SHPT prevalence after surgery [14].

Discussing the Role of Surgery Type

In our study, RYGB had slightly lower Ca levels when compared with the other 2 procedures probably due its greater impact on intestinal absorption, although this is not a statistically significant finding (Table 2). As RYGB consists on bypassing the duodenum and part of jejunum, the intestinal areas of Ca absorption, the resultant diminished Ca uptake is a powerful stimulus for PTH secretion [12] (that is not even higher due to 25-OH VitD supplementation of this group). Another interesting aspect was the increase in ALK-P among those submitted to RYGB. Considering that ALK-P encompass bone-specific ALK, this might reflect an increase in bone turnover to replenish Ca levels after this surgery [15, 16]. We also found the lower levels of 25-OH VitD and higher rates of 25-OH VitD deficiency among patients submitted to LAGB a little bit odd. Moreover, we were not expecting it to have the biggest proportion of patients with SHPT 1 year after surgery because it would be expected that would interfere less with absorptive processes of Ca and vitamin D [17]. The authors think that the explanation lies not on the surgical procedure itself but on 25-OH VitD supplementation. Our hospital does not perform LAGB since 2012 and, probably, the awareness for the importance of supplementation of these subjects was not so refined as it is nowadays (a fact that contributed to the lowest proportion of 25-OH VitD supplementation of the three types of surgery at 1 year). This poor 25-OH VitD supplementation among patients submitted to LAGB is one of the possible explanations to the occurrence of 25-OH VitD deficiency and SHPT 1 year after surgery. It is also noteworthy that RYGB had a greater proportion of patients with SHPT 1 year after surgery when compared with SG. This can be explained again by differential 25-OH VitD supplementation, but it might be also helped by the nature of surgical procedure and its impact on gastrointestinal tract.

Considerations About SHPT Prevalence and Patient's Characteristics According to SHPT Status

The rates of SHPT almost doubled between 1 year after and 4 years after surgery probably because, in our hospital, after 3 years of semesterly follow-up, the patients start to have 1 consultation per year until year 6 after surgery. Between the consultation of 3rd and 4th year, there is a period that relies on family physicians for the prescription of supplements and vitamin D and, sometimes, these therapies are stopped because these professionals are still not aware for the specific follow-up of these particular patients.

When we addressed the characteristics of patients with and without SHPH at baseline, we found a lower level of Ca and 25-OH VitD levels, despite the increased rates of 25-OH VitD and Ca. The higher PTH levels among these patients are expected as the result of low inhibitory effects of 25-OH VitD and low Ca levels, that function as a stimulus for PTH production. This aims to increase bone resorption and restore Ca plasmatic levels [18, 19]. The low 25-OH VitD and Ca levels despite higher supplementation rates only stresses the idea that the actual supplementation rates among patients with obesity and higher PTH levels probably is not enough to face this problem. The results of subjects with SHPT 1 year after surgery revealed increased levels of glucose and HbA1c. In SHPT with uremic disease, it has been hypothesized that PTH plays an important role in glucose homeostasis by promoting insulin resistance and decreased β cell function [20]. Despite our data being concordant with these findings, there is not, to our knowledge, any investigation regarding the influence of SHPT on glucose status among bariatric patients. Blood pressure also seems to be affected by SHPT 1 year after surgery. Again, despite the known mechanisms regarding increased arterial stiffness and hypertension among SHPT patients with chronic kidney disease, we found no data addressing the possible relation between SHPT and increased blood pressures in patients with obesity submitted to surgery. Interestingly, weigh loss is higher among patients with SPHT. It seems to be concordant with data regarding higher PTH with weight reduction, with indirectly may lead to bigger alterations on bone metabolism among these patients. This fact is supported by the increased ALK-P levels among patients with SHPT. As expected, 25-OH VitD levels are lower and 25-OH VitD deficiency proportion

was higher in subjects with SHPT, and this occurred despite increased 25-OH VitD supplementation.

Interestingly, at 4 years after surgery, there were no differences between groups regarding Ca, 25-OH VitD, phosphorus, or magnesium. A study regarding humans 6 to 8 months after RYGB found decreased expression of the calcium intestinal transporters on jejunal mucosa biopsies (TRPV6 transporters), which supports lower calcium absorption on the short term after surgery [21]. Despite this fact, mRNA expression of TRPV6 transporters were heavily increased in jejunum and ileum of rats 16 weeks after being submitted to RYGB (a late time point for these animals) [22]. This makes the authors believe that the intestinal mucosa may adapt over time to compensate the decreased ability to absorb calcium after surgery, narrowing differences between individuals. Despite these adaptations, subjects with SHPT still seem to have increased bone metabolic activity at 4 years (reflected by the higher ALK-P–94.6 vs 78.3 mg/dL, $p < 0.001$).

Discussing the Predictors of SHPT After Bariatric Surgery

When we studied the predictors of SHPT, we found that sex does not seem to predict SHPT while older age only does that 1 year after surgery. It is known that frequency of vitamin D deficiency increases with age mirroring the diminished production of vitamin D by the aging skin. Moreover, 1,25 OH vitamin D effect on calcium intestinal resorption is reduced by age [23]. The explanation to the fact that age does not predict SHPT at 4 years may reside on differential vitamin D supplementation or the age range of included patients. Lower 25-OH VitD levels predicted high PTH levels 1 year after surgery but not 4 years after surgery. The explanation is intricate and likely multifactorial, but it is probably related with long-term adaptations of the organism after bariatric surgery with impact on phosphocalcium metabolism. The only parameter that predicted SHPT at 1 and 4 years after surgery was RYGB, raising again the awareness for the important impact of this procedure on Ca, PTH, and 25-OH VitD complex relationships after surgery. This may have a long-term impact on bone that is supported in this study by the increased ALK-P as a predictor for SHPT at 4 years.

Strengths of this Study

This is one of the few articles that address SHPT after bariatric surgery considering the differences between three surgery types. In addition, it brings some clarification in relation to the predictors of secondary hyperparathyroidism after surgery, especially at 4 years. By doing this, it also highlights again the importance of aggressive 25-OH VitD supplementation, especially among bariatric patients submitted to RYGB.

Limitations of this Study

Limitations comprise the study retrospective design and absence of data regarding phosphocalcium metabolism at baseline, which only allowed to compare the impact of surgery type on a subgroup of patients. Also, information regarding sunlight exposure among groups was not available. In addition, there was considerable loss to follow up between the 1st and 4th year after surgery (76.4%). Other limitation lies on the fact that some of our assumed SHPT cases may, in fact, be non-diagnosed primary hyperparathyroidism (PHPT) cases. It is known that PHPT is associated with obesity and metabolic syndrome [24], but there is data revealing that PHPT is a rare occurrence among patients submitted to bariatric surgery (prevalence of 0.6% after RYGB according to one of the few papers addressing this matter [25]). For this reason, we believe that this limitation does not compromise the overall conclusions of our investigation. Moreover, the proportion of 25-OH VitD and Ca supplementation is based on information written on patient clinical files, which does not guarantee that they are effectively being taken by the patient. As presented on results, there is a very low Ca supplementation rate in our hospital, a factor that can have contributed to the high prevalence of SHPT in this population. Despite this, supplementation with calcium was not significantly different between groups after surgery. Finally, ALK-P is not a bone-specific marker and Ca is not the best parameter to evaluate for postoperative Ca deficiency because its levels are maintained relatively stable initially due to the increased bone metabolism [26]. Data regarding even longer follow-up periods are needed to study the impact of SHPT on fracture risk among different bariatric procedures.

Conclusion

The prevalence of SHPT is considerably higher before and 4 years after BS than 1 year after surgery. These findings seem to call into question the efficacy of the implemented follow-up plans of vitamin D supplementation on the long term, mainly among patients submitted to RYGB.

Acknowledgements We would like to thank the important contribution of several members of CRIO group: John Preto, Eduardo Lima da Costa, Hugo Sousa, André Pinho, Eva Lau, Selma Souto, Carla Galego, Flora Correia, Cidália Gil, Diva Melim, Eduardo Pinto, Marco Silva, Cristina Martins, Luis Miguel Pereira, Inês Magalhães, Isabel Brandão, Sertório Manuel Andrade, Patrícia Nunes.

Grant Support No grant support to declare.

Declarations

Ethics Approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to Participate For this type of study, formal consent is not required.

Conflict of Interest The authors declare that they have no conflict of interest.

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Article 3

Effects of Bariatric Surgery on Sarcopenic Obesity Outcomes: A One-Year Prospective Study in Middle-Aged Women.

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Obesity surgery journal

Published in 2024

Obesity Surgery (2024) 34:1674–1683
https://doi.org/10.1007/s11695-024-07164-x

ORIGINAL CONTRIBUTIONS

Effects of Bariatric Surgery on Sarcopenic Obesity Outcomes: A One-Year Prospective Study in Middle-Aged Women

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Received: 14 January 2024 / Revised: 4 March 2024 / Accepted: 6 March 2024 / Published online: 25 March 2024
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Abstract

Introduction Sarcopenic obesity (SO) is characterised by the confluence of muscle deterioration and high adiposity. When non-surgical interventions prove insufficient, bariatric surgery (BS) becomes the primary approach. This study aimed to address BS effects on SO outcomes 1 year post-surgery among middle-aged women, also considering physical exercise's impact.

Methods Prospective single-centre study of 140 patients who underwent Roux-en-Y gastric bypass or sleeve gastrectomy between November 2019 and December 2022. Participants were categorised into tertiles according to SO's diagnosis and severity (group 1—patients with the most severe SO; group 2—intermediate; group 3—the least severe or without SO), calculated considering the consensus issued by ESPEN and EASO in 2022. Evaluations of clinical and biochemical parameters were conducted before and 12 months after BS, and the variation was used for comparative purposes. Body composition was assessed using bone density scans. Linear regression analysis accounted for both surgery type and baseline body mass index (BMI).

Results Before BS, SO prevalence in the overall sample was 89.3%, decreasing to 2.9% after BS. Group 1 had more body fat mass (56.9 vs 54.8 vs 50.7 kg, $p < 0.001$), total, trunk and leg fat at baseline and a significantly lower total skeletal muscle mass (47.2 vs 49.4 vs 51.8 kg, $p < 0.001$). One year post-BS, group 1 presented more weight loss (− 39.8 ± 11.4 kg, $p = 0.031$), BMI reduction (− 15.9 ± 4.6 kg/m^2, $p = 0.005$) and lost more fat mass (− 32.6 vs − 30.5 vs − 27.9 kg, $p = 0.005$), but not total skeletal muscle mass (− 5.8 vs − 5.9 vs − 6.8 kg, $p = 0.130$). Remission rates for comorbidities were substantial among all groups, but more marked among patients within group 1 (type 2 diabetes mellitus 75%, hypertension 47.1% and dyslipidemia 52.8%). Engagement in physical exercise of any kind has increased post-BS (33.1% vs 79.1%).

Conclusion Despite concerns about malabsorptive mechanisms potentially worsening muscle loss, patients with the most severe SO undergoing BS lost more fat mass while experiencing the smallest reduction in total skeletal muscle mass. Remission rates for comorbidities following BS were notable among all groups.

Keywords Bariatric surgery · Sarcopenic obesity · Metabolic outcomes · Muscle mass · Weight loss · Physical exercise

Introduction

Sarcopenic obesity (SO), a condition initially described by Baumgartner in 2006 [1], has garnered considerable attention from the medical community in recent years. The confluence of muscle deterioration, encompassing low muscle mass and/or strength loss, and high adiposity, creates a synergistic health impact that transcends the consequences of either of these conditions, and that is the main reason for its increasing recognition as an entity itself. Regrettably, the absence of a universal consensus on diagnostic criteria has compounded the challenges faced in approaching this condition. To answer

***Pietra Rodrigues and Fernando Mendonça are both co-first authors and they contributed equally to this work.**

Key Points
- Bariatric surgery emerges as both a risk factor and a management approach in sarcopenic obesity.
- Patients with severe sarcopenic obesity lost more fat mass and less muscle mass after bariatric surgery.
- Bariatric surgery reduces sarcopenic obesity's prevalence and improves comorbidities.

this problem, the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) jointly issued a consensus statement addressing SO's definition, diagnostic procedures, and established cut-off values for diverse ethnic groups, sexes and age categories. This effort was undertaken in response to the limitations of the previously widely used consensus, the Revised European Working Group on Sarcopenia in Older People (EWGSOP2), which solely focused on an older population and was designed exclusively to address sarcopenia [2–4]. SO is strongly associated with a plethora of adverse health outcomes and comorbidities, including atherosclerosis, insulin resistance (IR), type 2 diabetes mellitus (DM2), hypertension (HT), dyslipidemia, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), heart failure (HF), osteoporosis and a higher mortality rate especially in women [5–7], bearing a substantial economic and biopsychological burden.

Studies suggest a reciprocal relationship between skeletal muscle and adipose tissue, exacerbated by factors like aging, malnutrition and sedentary lifestyle, triggering chronic inflammation, oxidative stress and IR in adipose tissue, which ultimately leads to muscle apoptosis, fat accumulation [8] and compromised bone health [9].

The management of SO should be approached in a multidisciplinary perspective, with dietary guidance and a combination of aerobic and resistance exercises constituting the primary intervention. However, the efficacy of these measures in the long term has, thus far, proven less than promising [10]. When both lifestyle modifications and medical therapies fall short, bariatric surgery (BS) emerges as the most viable option for morbidly obese individuals who meet the criteria, as it addresses the health-related comorbidities of SO [11]. Conversely, it has been proposed that bariatric surgery may have detrimental muscle effects in obese patients with diminished muscle mass or function, primarily due to the malabsorptive mechanisms involved, which are risk factors to SO, although its impact in women under the age of 65 remains relatively underexplored [3].

Thus, this study aims to assess the effects of BS on SO outcomes within a 1-year follow-up period in women, considering their metabolic parameters, the remission of multiple comorbidities (such as HT, DM2 and dyslipidemia) and the possible impact of physical exercise in SO's management.

Materials and Methods

Subjects and Study Design

This single-centre study employed a prospective design and involved the initial recruitment of 140 female participants who had undergone Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG), consecutively selected from November 2019 to December 2022 during pre-operative evaluation by the Integrated Responsibility Center for Obesity (CRIO group). The eligibility criteria for this study were the following: (a) women with obesity, aged 40–65 years; (b) meeting the criteria for BS, which included having a body mass index (BMI) of ≥ 35 kg/m^2 with at least one comorbidity such as metabolic syndrome, DM2, dyslipidemia, HT or cardiorespiratory disease, among others, or BMI of ≥ 40 kg/m^2 despite their comorbidities; (c) at least 1 year of non-surgical approaches to obesity, which had not resulted in satisfactory weight loss; and (d) obesity not attributable to classical endocrine diseases.

The exclusion criteria encompassed the following: (a) second or revisional BS; (b) weight exceeding 140 kg, the maximum weight supported by our dual-energy X-ray absorptiometry (DXA) equipment; (c) non-stabilized psychiatric illnesses or narcotic or alcohol dependence; (d) pharmacological therapy that could impact muscle mass, such as corticosteroids; and (e) having a severe clinical condition, including cardiovascular, pulmonary, hepatic, renal, osteoarticular and malignant neoplasms.

The choice of surgery technique was determined by the surgical team according to the best clinical practice**.** The study received approval from the ethics committee for health of our hospital centre (reference no. 276/2018).

Sarcopenic Obesity Classification and Cut-off Points

The definition and diagnosis of SO were based on the 2022 consensus proposed by ESPEN and EASO, which provides specific cut-off values suitable for our study population [3]. Body composition was assessed using DXA, with an increased percentage of fat mass (FM), considered as > 43% for Caucasian women [3, 12]. As for the reduced muscle mass, it was determined by the sum of the lean mass of arms and legs (appendicular lean mass (ALM)) adjusted to body weight (W) in accordance with the consensus recommendation for Caucasian women aged 18–65 years, which stipulates an ALM/W ratio < 23.47% [3, 13]. As an additional analysis, we also evaluated the study population according to tertiles of ALM/W (group 1—patients with the most severe SO; group 2—intermediate; group 3—the least severe or without SO).

Pre- and One Year Post-operative Evaluation

All evaluations were conducted both before and 12 months after bariatric surgery. The variation between those values was used for comparison between groups. Body composition was assessed by DXA using a properly calibrated densitometer (model Lunar iDXA). The studied parameters were body

fat, proportion of total fat mass, trunk fat mass and leg fat mass, arm lean mass, leg lean mass and bone mineral content (BMC). Other assessed paraments were bone mineral density, *T* score, *Z* score at the lumbar spine (L1–4), total femur, femoral neck and full body.

Anthropometric measurements were taken, including body weight, height, waist circumference and BMI. Blood pressure was measured during their Endocrinology appointments, with the patient seated for at least 5 min. Blood samples were collected after a fasting period of at least 12 h. Biochemical parameters analysed in our study included albumin, serum total protein (STP), total cholesterol (CT), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TG), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), iron, transferrin, ferritin, folic acid, vitamin B12, 25-OH-vitamin-D, total calcium, ionized calcium, phosphorus, magnesium (Mg), parathyroid hormone (PTH), thyroid-stimulating hormone (TSH), free thyroxine (T4L), fasting glucose (FG), insulin, hemoglobin A1c (HbA1c) and microalbuminuria. IR was assessed using the homeostasis model assessment for insulin resistance (HOMA-IR). Estimated glomerular filtration rate (eGFR) was calculated for all subjects using the 4-variable modification of diet in renal disease (MDRD) formula.

Information regarding medical history and comorbidities, medications in use, menopause history and supplementation prior and post-surgery was collected based on medical records. Physical exercise was retrospectively collected after surgery and included the type (aerobic, resistance training or both) and duration of activity (in minutes per week) before and after surgery.

The study also evaluated the presence of DM2, HT and dyslipidemia, both at baseline and after a 1-year follow-up period. DM2 was defined by a fasting glucose level ≥ 126 mg/dL or HbA1c level ≥ 6.5% or antidiabetic medication. HT was characterized by a systolic blood pressure (SBP) ≥ 140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg. The current use of antihypertensive medication was also diagnostic. Dyslipidemia was diagnosed by LDL ≥ 130 mg/dL, HDL ≤ 50 mg/dL, TG ≥ 150 mg/dL or CT ≥ 240 mg/dL. Participants under medication with statins or fibrates were also considered as dyslipidemic.

Remission of any of these comorbidities was considered when a patient diagnosed with a comorbidity during the preoperative period no longer met the diagnostic criteria 1 year post-bariatric surgery.

Statistical Analysis

Continuous variables with normal distribution were presented as means and standard deviations, being compared using one-way ANOVA. Continuous variables with non-normal distribution were described as medians and interquartile range, being compared using Kruskal-Wallis test. Categorical variables were expressed as percentages, being compared using a χ^2 test. Reported p values are two-tailed, and $p \leq 0.05$ was considered statistically significant. Linear regression models unadjusted and adjusted for surgery type (SG vs RYBG) and baseline BMI were performed to evaluate the predictors of outcomes at 12 months. Analyses were conducted with the use of STATA 18.0® software.

Results

A total of 140 female participants, with a mean age of 50.9 years old, mean weight of 107.9 kg and mean BMI of 42.1 kg/m^2, were enrolled in the study. The prevalence of SO, determined by specific cut-offs outlined by the ESPEN and EASO's consensus, was 89.3% in the overall sample before surgery and decreased to 2.9% 1 year post-BS. Most participants underwent RYGB (n = 100, 71.4%). Patient stratification into three groups was conducted, with group 1 being defined as the lowest tertile of subjects (the most severe degree of SO). The baseline characteristics of both the overall sample and the three individual groups are presented in Table 1.

Only 33.1% of participants engaged in any form of physical exercise before surgery, while 79.1% were doing some type of exercising after the follow-up period. The duration of their exercise regimen, measured in minutes per week, exhibited an increase across all groups following surgery, although without statistical significance. Notably, both before and after BS, group 1 individuals allocated more time per week to augment their physical exercise levels, when compared to the other tertiles (Supplementary Table 1). However, concerning the nature of physical exercise 1 year post-BS, only 20.1% of the total sample engaged in both aerobic and resistance training. This still marked an improvement from the baseline rate (6.5%). Remarkably, group 1 showed a tendency towards increased engagement in combined aerobic and resistance training compared to the other groups (23.4% vs 19.6% vs 17.4%, $p = 0.090$), yet most participants who exercised primarily focused on solo aerobic exercises (54.0%).

Anthropometric parameters, blood pressure and body composition at baseline and 1 year after BS are presented in Table 2. At baseline, group 1 exhibited an increased proportion of total fat, trunk fat and leg fat compared to other groups, the same occurring with body fat mass (56.9 ± 8.8 vs 54.8 ± 7.2 vs 50.7 ± 8.4 kg, $p < 0.001$). Group 1 also demonstrated significantly lower total skeletal muscle mass (47.2 ± 5.5 vs 49.4 ± 5.0 vs 51.8 ± 5.8 kg, $p < 0.001$). Regarding bone parameters on DXA, none were statistically

Table 1 Baseline characteristics of the overall sample and comparison among participants categorized into tertiles

Variable	Overall sample (*n* = 140)	Group 1 (*n* = 47)	Group 2 (*n* = 47)	Group 3 (*n* = 46)	Pvalue
Age*	50.9 ± 7.0	51.9 ± 7.3	50.7 ± 6.7	50.2 ± 7.1	0.250
Weight (kg)*	107.9 ± 13.2	109.1 ±14.7	108.6 ± 11.7	106.0 ± 13.2	0.270
BMI (kg/m^2)*	42.1 ± 4.6	43.4 ± 5.6	42.1 ± 3.6	40.6 ± 3.9	**0.004**
Waist circumference (cm)*	118.5 ± 10.5	121.4 ± 8.2	121.2 ± 10.2	113.9 ± 11.0	**0.023**
Surgical procedure					0.600
RYGB, *n* (%)	100 (71.4)	34 (72.3)	35 (74.5)	31 (67.4)	
SG, *n* (%)	40 (28.6)	13 (27.7)	12 (25.5)	15 (32.6)	
Sarcopenic obesity, *n* (%)	125 (89.3)	47 (100.0)	47 (100.0)	31 (67.4)	**<0.001**
SBP (mmHg)	140.3 ± 16.7	140.7 ± 20.4	140.6 ± 16.9	139.7 ± 13.3	0.830
DBP (mmHg)	86.5 ± 10.8	86.0 ± 11.3	84.8 ± 11.2	88.8 ± 9.7	0.330
Menopause, *n* (%)	72 (51.4)	26 (55.3)	25 (53.2)	21 (45.7)	0.360
DM2, *n* (%)	41 (29.3)	12 (25.5)	11 (23.4)	18 (39.1)	0.150
HT, *n* (%)	98 (70.0)	34 (72.3)	31 (66.0)	33 (71.7)	0.950
Dyslipidemia, *n* (%)	110 (78.6)	36 (76.6)	38 (80.9)	36 (78.3)	0.840

BMI body mass index, *RYGB* Roux-en-Y gastric bypass, *SG* vertical sleeve gastrectomy, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *DM2* type 2 diabetes mellitus, *HT* hypertension

*Data are expressed as mean ± SD

significant 1 year after BS, although group 1 displayed slightly diminished BMC at baseline (2.5 ± 0.3 vs 2.6 ± 0.3 vs 2.7 ± 0.3 g, $p = 0.004$). One year after BS, there has been an anthropometric difference between groups regarding both their weight ($p = 0.031$), showing a mean reduction of 39.8 kg in group 1, and BMI ($p = 0.005$), with a mean reduction of 15.9 kg/m^2 in this same group. Although all groups exhibited decreased fat-related parameters, only body fat mass, leg fat (%)and both arm and leg lean masses reached statistical significance. Notably, group 1 lost more fat mass compared to other groups (− 32.6 ± 8.6 vs − 30.5 ± 7.3 vs − 27.9 ± 7.6 kg, $p = 0.005$), but did not experience a greater reduction in their total skeletal muscle mass. In fact, group 1 had a mean variation of − 5.8 kg of total skeletal muscle mass (vs − 5.9 vs − 6.8 kg, $p = 0.130$).

To mitigate potential disparities in our primary body composition findings that may stem from the type of surgery conducted, the authors conducted a comparative analysis of the 1-year variation in weight, BMI, fat and lean mass induced by restrictive and malabsorptive surgeries across the entire sample. Patients undergoing RYGB displayed more pronounced reductions in all parameters. However, statistical significance was observed solely in the differences in fat mass when comparing SG and RYGB (− 26.7 ± 9.1 vs − 31.9 ± 7.0, $p \leq 0.001$) (Supplementary Table 2).

A comparison of laboratory parameters has been performed at Table 3. At baseline, group 1 had a higher eGFR compared to the overall sample (mean difference of 5.6 mL/min/1.73 m^2, $p = 0.019$), and so did TSH, although within the physiological range (2.6 ± 3.0 vs 1.7 ± 0.8 vs 1.6 ± 0.7, $p = 0.017$). After 1 year, both Mg and TSH showed statistically significant changes, with group 1 exhibiting a larger decrease in TSH values (− 1.0 ± 3.0 µUI/mL, $p = 0.006$), but no differences were found regarding T4L ($p = 0.610$). There was improvement in CT, HDL, LDL and TG levels in all groups, with group 1 showing the most significant improvement in CT levels (although being non-statistically significant). Regarding FG, HbA1c, HOMA-IR and insulin, all groups presented some metabolic improvement, but also not enough to be considered significant. As for iron's metabolism, there has been an increase after surgery in iron and ferritin levels, both being slightly more pronounced in the most severe group. AST showed increased levels in all groups after surgery when compared to baseline, especially in group 1 (7.1 ± 15.8 vs 3.9 ± 19.1 vs 0.4 ± 12.7, $p = 0.05$). During the follow-up period, there has been an increase in vitamin B12 and 25-OH-vitamin-D levels within group 1.

A detailed breakdown of multivitamin and mineral supplement usage is presented in Supplementary Table 3, providing a better insight into these findings. Of participants in group 1, 42.6% were receiving 25-OH-vitamin-D supplementation following surgery, while 19.1% were under vitamin B12 supplementation. None of the variables related to supplement usage exhibited statistical significance.

Table 4 presents the assessment of comorbidities 1 year post-surgery, indicating a notable remission rate for DM2, HT and dyslipidemia in all groups, regardless of the absence of statistically significant differences between them. Despite this fact, there was a tendency for increased dyslipidemia remission in group 1, with a remission rate of 52.8%

Table 2 Comparative analysis of anthropometric parameters, blood pressure and body composition assessed by DXA at baseline and 1 year after BS

Variable	Baseline				P value	Variation one year after BS			P value
	Overall Sample (n = 140)	Group 1 (n = 47)	Group 2 (n = 47)	Group 3 (n = 46)		Group 1 (n = 47)	Group 2 (n = 47)	Group 3 (n = 46)	
Weight (kg)	107.9 ± 13.2	109.1 ±14.7	108.6 ± 11.7	106.0 ± 13.2	0.270	-39.8 ± 11.4	-38.3 ± 9.6	-35.3 ± 9.1	**0.031**
BMI (kg/m^2)	42.1 ± 4.6	43.4 ± 5.6	42.1 ± 3.6	40.6 ± 3.9	**0.004**	-15.9 ± 4.6	-14.8 ± 3.5	-13.6 ± 3.4	**0.005**
SBP (mmHg)	140.3 ± 16.7	140.7 ± 20.4	140.6 ± 16.9	139.7 ± 13.3	0.830	-7.8 ± 21.4	-9.8 ± 28.5	-17.3 ± 15.8	0.250
DBP (mmHg)	86.5 ± 10.8	86.0 ± 11.3	84.8 ± 11.2	88.8 ± 9.7	0.330	-13.0 ± 17.7	-12.1 ± 16.1	-19.3 ± 14.1	0.250
BMC (g)	2.6 ± 0.3	2.5 ± 0.3	2.6 ± 0.3	2.7 ± 0.3	**0.004**	-0.2 ± 0.1	-0.2 ± 0.1	-0.2 ± 0.1	0.120
Body fat mass (kg)	54.2 ± 8.5	56.9 ± 8.8	54.8 ± 7.2	50.7 ± 8.4	**<0.001**	-32.6 ± 8.6	-30.5 ± 7.3	-27.9 ± 7.6	**0.005**
Total body fat (%)	52.2 ± 3.5	54.6 ± 2.6	52.6 ± 2.8	49.3 ± 3.0	**<0.001**	-18.3 ± 6.6	-17.5 ± 6.2	-16.3 ± 5.9	0.130
Trunk fat (%)	55.9 ± 3.8	58.1 ± 2.9	56.3 ± 3.2	53.3 ± 3.6	**<0.001**	-22.5 ± 8.4	-22.1 ± 8.2	-20.8 ± 7.7	0.340
Legs fat (%)	49.2 ± 5.5	52.0 ± 5.0	49.8 ± 4.9	45.7 ± 4.8	**<0.001**	-14.1 ± 5.4	-12.6 ± 5.1	-11.3 ± 4.9	**0.012**
Total skeletal muscle mass (kg)	49.4 ± 5.7	47.2 ± 5.5	49.4 ± 5.0	51.8 ± 5.8	**<0.001**	-5.8 ± 2.5	-5.9 ± 3.2	-6.8 ± 2.9	0.130
Arms lean mass (kg)	5.5 ± 1.2	4.7 ± 0.9	5.7 ± 1.2	6.0 ± 1.0	**<0.001**	-0.3 ± 0.8	-0.9 ± 1.2	-0.9 ± 0.8	**0.010**
Legs lean mass (kg)	17.4 ± 2.6	16.3 ± 2.3	17.4 ± 2.1	18.7 ± 2.8	**<0.001**	-3.0 ± 1.2	-3.2 ± 1.4	-3.8 ± 1.6	**0.006**
L1-L4 BMD (g/cm^2)	1.2 ± 0.2	1.2 ± 0.1	1.2 ± 0.2	1.2 ± 0.1	0.620	-0.0 ± 0.1	-0.1 ± 0.1	-0.1 ± 0.1	0.330
L1-L4 T-score	0.3 ± 1.2	0.3 ± 1.1	0.3 ± 1.3	0.3 ± 1.1	0.700	-0.4 ± 0.6	-0.5 ± 0.5	-0.5 ± 0.6	0.540
L1-L4 Z-score	-0.0 ± 1.2	-0.0 ± 1.1	-0.1 ± 1.4	-0.1 ± 1.2	0.840	0.7 ± 0.6	0.6 ± 0.6	0.5 ± 0.6	0.090
Femoral neck BMD (g/cm^2)	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.1 ± 0.1	0.130	-0.1 ± 0.1	-0.1 ± 0.1	-0.1 ± 0.1	0.910
Femoral neck *T*-score	0.5 ± 1.1	0.4 ± 1.1	0.2 ± 1.0	0.8 ± 1.2	0.110	-0.3 ± 0.9	-0.5 ± 1.1	0.0 ± 0.8	0.060
Femoral neck *Z*-score	0.2 ± 1.0	-0.0 ± 1.1	-0.1 ± 1.4	-0.1 ± 1.2	0.840	0.3 ± 0.9	0.0 ± 0.9	0.4 ± 0.8	0.550
Total femur BMD (g/cm^2)	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	0.220	-0.1 ± 0.1	-0.1 ± 0.1	-0.1 ± 0.1	0.570
Total femur *T*-score	1.5 ± 1.2	1.5 ± 1.2	1.3 ± 1.2	1.8 ± 1.0	0.200	-0.9 ± 0.5	-1.0 ± 0.5	-1.0 ± 0.5	0.290
Total femur *Z*-score	1.0 ± 1.1	1.0 ± 1.1	0.8 ± 1.2	1.2 ± 0.9	0.400	-0.1 ± 0.4	-0.2 ± 0.5	-0.3 ± 0.6	0.060
Total body BMD (g/cm^2)	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	0.970	-0.1 ± 0.1	-0.1 ± 0.0	-0.0 ± 0.1	0.640
Total body *T*-score	1.8 ± 1.1	1.8 ± 1.1	1.8 ± 1.1	1.8 ± 1.0	0.970	-0.5 ± 0.6	-0.6 ± 0.4	-0.5 ± 0.5	0.490
Total body *Z*-score	0.5 ± 1.0	0.6 ± 1.0	0.5 ± 1.0	0.5 ± 0.9	0.750	0.8 ± 0.6	0.7 ± 0.6	0.7 ± 0.8	0.310

All data in this table are expressed as mean ± SD

BS bariatric surgery, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMC* bone mineral content, *L1–L4* lumbar spine from 1 to 4, *BMD* bone mineral density

Table 3 Comparative analysis of laboratory parameters at baseline and 1 year after BS

Variable	Baseline				P value	Variation 1 year after BS			P value
	Overall sample (*n* = 140)	Group 1 (*n* = 47)	Group 2 (*n* = 47)	Group 3 (*n* = 46)		Group 1 (*n* = 47)	Group 2 (*n* = 47)	Group 3 (*n* = 46)	
STP (g/L)*	70.6 ± 4.5	70.6 ± 3.9	69.8 ± 4.8	71.4 ± 4.7	0.410	-4.8 ± 3.6	-4.1 ± 4.5	-3.1 ± 4.2	0.060
Albumin (g/L)*	40.6 ± 2.5	40.4 ± 2.0	40.7 ± 3.1	40.8 ± 2.3	0.460	-0.6 ± 2.1	-0.8 ± 2.7	-0.5 ± 2.0	0.910
FG (mg/dL)**	103.0 [94.0, 119.0]	106.0 [98.0, 118.0]	101.0 [93.0, 110.0]	112.0 [94.0, 123.0]	0.660	-19.3 ± 32.3	-7.8 ± 32.0	-26.2 ± 47.7	0.410
HbA1c (%)**	5.8 [5.5, 6.0]	5.6 [5.4, 5.9]	5.9 [5.6, 6.1]	5.7 [5.5, 6.0]	0.520	-0.6 ± 0.6	-0.5 ± 0.4	-0.7 ± 1.1	0.340
HOMA-IR**	5.1 [3.1, 7.1]	5.1 [2.3, 6.5]	4.8 [3.3, 7.1]	5.2 [3.2, 9.4]	0.160	-3.4 ± 3.7	-3.6 ± 2.6	-5.7 ± 12.3	0.150
Insulin (µU/mL)**	19.6 [13.0, 25.7]	17.9 [9.2, 23.8]	19.6 [13.1, 26.4]	20.5 [13.8, 27.6]	0.130	-11.0 ± 11.6	-13.4 ± 8.7	-16.6 ± 29.2	0.150
CT (mg/dL)*	190.8 ± 46.2	189.0 ± 38.7	188.3 ± 35.5	195.4 ± 61.8	0.520	-25.1 ± 33.2	-23.4 ± 34.8	-20.7 ± 53.9	0.620
HDL (mg/dL)*	51.6 ± 11.2	51.8 ± 9.3	51.5 ± 12.1	51.3 ± 12.3	0.810	4.0 ± 6.7	3.6 ± 7.2	6.1 ± 9.8	0.220
LDL (mg/dL)*	114.1 ± 36.6	111.0 ± 32.1	114.3 ± 26.6	117.0 ± 48.9	0.440	-19.9 ± 30.1	-21.3 ± 29.7	-17.2 ± 42.2	0.720
TG (mg/dL)**	109.0 [83.0, 154.0]	120.0 [87.0, 151.0]	102.0 [77.0, 126.0]	109.0 [87.0, 170.0]	0.920	-47.1 ± 51.9	-28.7 ± 46.2	-59.2 ± 89.0	0.400
GGT (U/L)*	25.0 [18.0, 38.0]	26.0 [18.0, 44.0]	23.5 [16.0, 34.0]	25.0 [18.0, 38.0]	0.780	-9.2 ± 43.9	-10.0 ± 10.8	-27.5 ± 98.0	0.170
ALP (U/L)*	78.0 [65.0, 95.0]	78.5 [65.0, 95.0]	79.0 [61.0, 100.0]	75.0 [65.0, 93.0]	0.960	0.5 ± 22.4	0.2 ± 19.4	-5.4 ± 19.0	0.180
AST (U/L)*	20.0 [17.0, 26.0]	19.0 [16.0, 28.0]	21.0 [18.0, 26.0]	20.5 [16.0, 27.0]	0.430	7.1 ± 15.8	3.9 ± 19.1	0.4 ± 12.7	**0.050**
ALT (U/L)*	22.0 [16.0, 29.5]	19.5 [16.0, 28.0]	23.0 [19.0, 30.0]	22.0 [16.0, 30.0]	0.540	7.8 ± 23.9	5.7 ± 35.5	-0.7 ± 16.9	0.140
eGFR (mL/min/1.73 m^2)*	108.7 ± 24.4	114.3 ± 31.6	109.0 ± 18.4	102.2 ± 19.8	**0.019**	-5.9 ± 23.8	0.2 ± 16.9	1.5 ± 13.5	0.060
Microalbuminuria (mg/L)**	8.7 [4.6 ,20.8]	13.6 [4.8, 23.0]	9.0 [4.7, 23.8]	6.8 [4.3, 15.0]	0.120	-12.0 ± 51.2	1.1 ± 66.2	-7.1 ± 28.9	0.660
Iron (µg/dL)*	77.5 ± 27.0	76.0 ± 23.8	82.0 ± 27.3	74.0 ± 30.0	0.780	8.6 ± 30.0	0.2 ± 33.8	1.5 ± 13.5	0.060
Transferrin (mg/dL)*	275.0 ± 43.6	271.2 ± 42.5	266.6 ± 40.2	288.9 ± 46.3	0.070	-37.3 ± 34.0	-29.2 ± 34.5	-43.1 ± 63.9	0.590
Ferritin (ng/mL)**	77.5 [39.7, 169.9]	80.8 [50.0, 160.1]	82.6 [40.7, 180.8]	65.9 [29.6, 173.5]	0.450	28.3 ± 53.7	13.7 ± 64.2	12.3 ± 66.2	0.220
Folic acid (ng/mL)*	6.6 ± 3.5	6.8 ± 4.4	6.9 ± 3.4	6.1 ± 2.4	0.390	5.0 ± 5.5	5.0 ± 5.2	5.8 ± 4.9	0.540
Vitamin B12 (pg/mL)*	388.0 ± 215.4	378.3 ± 270.2	387.8 ± 129.3	399.1 ± 228.0	0.650	20.9 ± 221.4	-76.3 ± 156.6	-48.8 ± 229.6	0.100
Vitamin D (ng/mL)*	19.7 ± 8.6	19.2 ± 7.5	19.0 ± 8.2	21.0 ± 10.1	0.330	10.1 ± 13.7	9.0 ± 12.3	7.5 ± 12.4	0.330
P+ (mg/dL)*	3.3 ± 0.5	3.4 ± 0.5	3.3 ± 0.5	3.3 ± 0.4	0.590	0.4 ± 0.5	0.7 ± 0.5	0.6 ± 0.5	0.190
Total Ca (mEq/L)*	4.7 ± 0.2	4.7 ± 0.1	4.7 ± 0.2	4.7 ± 0.2	0.990	0.0 ± 0.2	0.0 ± 0.2	0.1 ± 0.2	0.200
Ionized Ca (mEq/L)*	2.5 ± 0.1	2.5 ± 0.1	2.5 ± 0.1	2.5 ± 0.1	0.810	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.2	0.680
Mg (mEq/L)*	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.2	1.6 ± 0.1	0.740	-0.0 ± 0.1	0.0 ± 0.1	0.1 ± 0.1	**0.003**
PTH (pg/mL)*	56.2 ± 21.5	54.9 ± 21.1	58.0 ± 17.6	55.6 ± 25.6	0.860	-4.0 ± 20.4	-8.3 ± 16.9	-8.4 ± 21.0	0.280
T4L (ng/dL)*	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	0.9 ± 0.1	0.980	0.1 ± 0.1	0.0 ± 0.1	0.0 ± 0.1	0.610
TSH (µUI/mL)*	2.0 ± 1.9	2.6 ± 3.0	1.7 ± 0.8	1.6 ± 0.7	**0.017**	-1.0 ± 3.0	-0.2 ± 0.7	0.1 ± 1.2	**0.006**

BS bariatric surgery, *STP* serum total protein, *FG* fasting glucose, *HbA1c* hemoglobin A1c, *HOMA-IR* homeostatic model assessment for insulin resistance, *CT* total cholesterol, *HDL* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol, *TG* triglycerides, *GGT* gamma-glutamyltransferase, *ALP* alkaline phosphatase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *eGFR* estimated glomerular filtration rate, *P+* phosphorus, *Ca* plasmatic calcium, *Mg* magnesium, *PTH* parathyroid hormone, *T4L* free thyroxine, *TSH* thyroid-stimulating hormone

*Data in this table are expressed as mean ± SD

**Data in this table are expressed as **median [min, max]

Table 4 Assessment of comorbidity remission 1 year after BS

Variable	Remission one-year after BS			P value
	Group 1	Group 2	Group 3	
DM2 remission, *n* after/*n* baseline (%)*	9/12 (75.0)	5/11 (45.5)	13/18 (72.2)	0.990
HT remission, *n* after/*n* baseline (%)*	16/34 (47.1)	14/31 (45.2)	23/33 (69.7)	0.070
Dyslipidemia remission, *n* after/*n* baseline (%)*	19/36 (52.8)	15/38 (39.5)	12/36 (33.3)	0.100

BS bariatric surgery, *DM2* type 2 diabetes mellitus, *HT* hypertension

*The symbol '/' represents a fraction used to denote the ratio between the number of individuals with the disease at the 1-year follow-up evaluation and the baseline number

Table 5 Linear regression analysis adjusted to BMI and type of BS surgery

Variable	95.0% Confidence interval			
	Coefficient	P value	Lower bound	Upper bound
Weight (kg)	.206	0.802	− 1.418	1.830
BMI (kg/m^2)	.307	0.312	− .292	.906
Mg (mEq/L)	.038	**0.003**	.0130	.064
TSH (µUI/mL)	.580	**0.007**	.160	1.000
Body fat mass (kg)	1.212	0.090	− .190	2.615
Leg fat (%)	1.283	**0.020**	.200	2.364
Arm lean mass (kg)	− .383	**<0.001**	− .579	− .188
Leg lean mass (kg)	− .564	**<0.001**	− .837	− .292

BS bariatric surgery, *BMI* body mass index, *Mg* magnesium, *TSH* thyroid-stimulating hormone

compared to 39.5% and 33.3% in the other two groups (p = 0.100).

After linear regression analysis adjustment for baseline BMI and type of surgery, only Mg, TSH, leg fat (%) and both lean masses remained statistically significant 1 year after BS (Table 5).

Discussion

In the present study, we aimed to evaluate the influence of bariatric surgery on sarcopenic obesity outcomes after a 1-year follow-up period in middle-aged women.

The consensus by ESPEN and EASO highlights that severe obesity correlates strongly with chronic non-communicable diseases. This correlation significantly impacts muscle anabolism and catabolism, with sedentarism being both a cause and a consequence of SO [3]. Managing these cases requires a multidisciplinary approach, where BS stands out for weight loss after failed non-surgical attempts. However, weight reduction post-BS often leads to muscle mass loss, especially in patients with additional health issues, which could worsen SO outcomes. Interestingly, the prevalence of SO seems consistent across different age groups, emphasizing the imperative need for universal management strategies [14].

To address SO after BS, careful monitoring of nutrition, suitable supplementation and tailored exercise programs are crucial. Yet, the main challenge lies in the varying definitions, thresholds and the absence of consensus on ideal body composition assessment methods [15–18]. This lack of clarity not only complicates diagnosis for physicians but also hampers the comparison of research findings, crucial for advancing global understanding and care for SO patients. The results of our study demonstrate that SO's prevalence is enormous among participants prior to BS, decreasing substantially after surgery. Our results contrast with some previous studies. For example, Sousa-Santos et al. [19] reported rates of 4.4% in Portugal using EWGSOP2 criteria, primarily observed in an older population. However, when comparing our study results with more recent studies using the 2022 ESPEN and EASO consensus, with cut-offs well determined for women within our age range and ethnicity, our results align more closely. An abstract published by Esposito et al. in April 2023, attempting to develop a valid SO screening tool for BS candidates, identified 99.4% of female participants as having SO [20].

Bariatric surgery did not have a deleterious impact in SO outcomes after a 1-year follow-up, as it could have had regarding worsening muscle mass loss in those patients. In fact, it helped induce SO remission in most participants, improving their body composition and metabolic parameters and mitigating comorbidities. Our follow-up period was decided based on previous research that demonstrated that the biggest changes in body composition following BS occurred in the first year [21], and the most important changes in total skeletal muscle mass and lean mass occurred especially within the initial 6 months [22, 23]. Our results showed that group 1 had a higher body fat mass and a lower total skeletal muscle mass prior to surgery, which is in line with previous research in this field and with the diagnostic criteria of SO [5, 24, 25]. Our study also showed that there was a high weight loss and a significant reduction in BMI and body fat mass, while there has been no statistically significant change in total skeletal muscle mass loss

among our tertiles. This appears as an important outcome, since muscle mass loss was a main concern of ours, especially regarding group 1, which is the most severe group. BS appears as a risk factor for SO, contributing to muscle loss [3, 26], but our findings acknowledge bariatric surgery as a safe and emerging strategy in SO patients, being in line with previous research works [5, 23, 27]. Thus, health benefits of BS in weight reduction and SO outcomes seem to occur predominantly at the expense of fat mass alone and less by compromising lean mass [5, 23, 27].

However, there has been a statistically significant change in arm and leg lean mass in our study. Surprisingly, the most severe tertile (group 1) was the one that lost less lean mass post-surgery. The authors believe that this might be due to the increasing rate of the combination between aerobic and resistance training in that group during the follow-up period, and this fact may reduce nuclear FOXO1 protein level, therefore diminishing muscle atrophy [28]. Physical exercise is one of the first-line approaches to SO, since it increases myogenesis and interleukins 6, 10 and 15, stimulates brown fat tissue, while reducing white fat and inflammatory factors (myostatin, FOXO, leptin, resistin, NF-KB). The combined effect results in a decrease in adipose tissue and inflammation, and an increase in protein synthesis [29].

The surgical intervention led to improved metabolic markers and reduced comorbidities in women across all groups, aligning with earlier research [5, 25, 30, 31] that links significant weight loss post-surgery to reduced oxidative stress, improved insulin resistance and better lipid profiles, potentially contributing to a substantial remission rate of DM2 in those with more severe SO [32–34]. BS has also shown superior results over medical treatments in reversing dyslipidemia, significantly reducing cardiovascular risk [21]. However, HT remission rates were lower in group 1 compared to the less severe groups, albeit not statistically significant. This aligns with previous studies linking morbid obesity to hypertension [35], but it shows variability in associating SO with this condition due to inconsistent definitions [36, 37], leading to conflicting outcomes.

Within our study, TSH showed significance at baseline, displaying higher values within group 1, and a more pronounced decrease post-BS, remaining within the physiological range.

Previous longitudinal studies in obese or sarcopenic populations provide some insights, although showing conflicting associations between thyroid function and body composition. For instance, Itterman et al. identified a positive correlation between TSH levels and increases in both BMI and waist circumference across adults aged 20 to 90 [38]. In agreement to that, other population-based studies were able to demonstrate that a decline in TSH levels was associated with a decrease in body weight [39–41]. Our findings are consistent with these studies.

Strengths of This Study

Our study, utilizing the ESPEN/EASO criteria, pioneers the longitudinal evaluation of middle-aged women regarding SO post-BS, an area that remains largely unexplored. Moreover, our study boasts a robust sample size, enhancing the potential applicability of our findings, particularly among women.

In addition, this investigation used DXA as the primary assessment tool, as favoured by ESPEN and EASO consensus given its superior accuracy when compared to bioelectrical impedance analysis [3].

Limitations of This Study

Our study faced several limitations that warrant consideration. Notably, we did not assess skeletal muscle function parameters. Furthermore, our study encountered notable missing values for certain variables, such as SBP and waist circumference, both displaying high missing rates at baseline (42.86% and 60% at baseline, respectively) and during follow-up (69.29% missing rates for SBP variation at 1 year follow-up). The COVID-19 pandemic significantly contributed to these missing values, disrupting follow-up appointments that were crucial for this assessment.

Another limitation is our exclusive focus on a female cohort due to the substantial predominance of women (85%) over males (15%) undergoing BS at our institution. However, while not fully elucidated, there is growing evidence suggesting that SO may portend a more adverse prognosis in women [42, 43].

Conclusion

Bariatric surgery emerges as a promising approach for middle-aged female patients with SO. Despite concerns about potential suboptimal outcomes due to malabsorptive mechanisms that may exacerbate muscle loss and therefore worsen the condition, the most severe group of patients with SO lost more fat mass and simultaneously experienced the smallest reduction in their total skeletal muscle mass, when compared to the less severe groups. Nonetheless, remission rates for comorbidities following BS were notable. A comprehensive assessment is necessary to accurately determine the substantial impact of physical exercise on enhancing the management and outcomes of SO following BS.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11695-024-07164-x.

Declarations

Ethics Approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Written informed consent was obtained from all individual participants included in the study.

Conflict of Interest The authors declare no competing interests.

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Supplementary Tables:

Supplementary Table 1: Comparative analysis of physical activity at baseline and one-year after BS

Variable	Baseline					One-year after BS				
	Overall sample (n=140)	Group 1 (n=47)	Group 2 (n=47)	Group 3 (n=46)	P value	Overall Sample (n=140)	Group 1 (n=47)	Group 2 (n=47)	Group 3 (n=46)	P value
Physical Exercise, n (%)	46 (33.1)	17 (36.2)	15 (32.6)	14 (30.4)	0.560	110 (79.1)	41 (87.2)	36 (78.3)	33 (71.7)	0.070
Type of Physical Exercise					0.470					0.090
Aerobic,n(%)	37(26.6)	15(31.9)	11(23.9)	11(23.9)		75(54.0)	29(61.7)	23(50.0)	23(50.0)	
Resistance Training, n (%)	1 (0.7)	0 (0.0)	1 (2.2)	0 (0.0)		6 (4.3)	1 (2.1)	4 (8.7)	1 (2.2)	
Aerobic+Resistance, n (%)	9 (6.5)	3 (6.4)	3 (6.5)	3 (6.5)		28(20.1)	11 (23.4)	9 (19.6)	8 (17.4)	
Time of Physical Exercise per week (minutes) *	120.0 [90.0, 270.0]	150.0 [90.0, 300.0]	135.0 [90.0, 300.0]	90.0 [80.0, 180.0]	0.250	180.0 [120.0, 300.0]	210.0 [120.0, 300.0]	180.0 [112.5, 240.0]	150.0 [120.0, 270.0]	0.430

*Time of physical exercise per week is expressed as median [min, max].

Supplementary Table 2: Comparative analysis of body composition variation at one year following restrictive (SG) and hypoabsorptive (RYGB) surgery in the overall sample

Variable	SG (n=40)	RYGB (n=100)	P value
Weight (kg) *	-35.5 ± 13.3	-38.9 ± 8.3	0.080
BMI (kg/m^2) *	-13.9 ± 5.3	-15.2 ± 3.3	0.100
Fat mass (kg) *	-26.7 ± 9.1	-31.9 ± 7.0	**<0.001**
Lean mass (kg) *	-5.9 ± 2.8	-6.2 ± 2.9	0.620

*Data are expressed as mean ± SD. Abbreviations: *RYGB* roux-en-Y gastric bypass, *SG* vertical sleeve gastrectomy, *BMI* body mass index.

Supplementary Table 3: Comparative analysis of multivitamin and mineral supplements at baseline and one-year after BS

Variable	Baseline				One-year after BS			
	Group 1 (n=47)	Group 2 (n=47)	Group 3 (n=46)	P value	Group 1 (n=47)	Group 2 (n=47)	Group 3 (n=46)	P value
Multivitamin-mineral *	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0		6.7 ± 2.7	6.9 ± 2.5	7.1 ± 2.4	0.520
Iron, n (%)	0 (0.0)	0 (0.0)	1 (2.2)	0.220	7 (14.9)	6 (13.0)	9 (19.6)	0.540
Vitamin D, n (%)	1 (2.1)	0 (0.0)	2 (4.3)	0.470	20 (42.6)	14 (31.1)	22 (47.8)	0.610
Vit B12, n (%)	0 (0.0)	0 (0.0)	0 (0.0)		9 (19.1)	5 (10.9)	8 (17.4%)	0.810
Mg, n (%)	0 (0.0)	0 (0.0)	1 (2.2)	0.220	4 (8.5)	5 (10.9)	8 (17.4)	0.190
Ca, n (%)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	

*Multivitamin-mineral is expressed as mean ± SD. Abbreviations: *Mg* magnesium, *Ca* calcium

Article 4

Impact of Menopausal Status on Bone Metabolism and Body Composition After Metabolic-Bariatric Surgery: A Two-year Prospective Study in Middle-Aged Women.

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Obesity Surgery

Published in 2026.

Obesity Surgery
https://doi.org/10.1007/s11695-026-08565-w

RESEARCH

Impact of Menopausal Status on Bone Metabolism and Body Composition After Metabolic-Bariatric Surgery: a Two-Year Prospective Study in Middle-Aged Women

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Received: 31 August 2025 / Revised: 15 February 2026 / Accepted: 24 February 2026
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Abstract

Introduction The impact of menopausal status on metabolic and densitometric outcomes following metabolic-bariatric surgery (MBS) remains insufficiently characterized. This study aims to evaluate the association between menopausal status at the time of MBS and changes in bone mineral density (BMD) and body composition.

Methods Prospective, single-center study including 162 patients undergoing MBS either Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG), between November/2019 and December/2022. Participants were divided into two groups based on menopause status at the time of surgery. Clinical and biochemical parameters were assessed preoperatively and at 6-, 12-, and 24-month post-surgery. Linear and logistic regression analyses were performed, adjusting for age, type of surgery, and baseline body mass index.

Results Postmenopausal patients showed a higher prevalence of T2D, hypertension and osteopenia. Two years after MBS, postmenopausal patients revealed to have a steeper decrease in bone mineral content (-0.31 ± 0.13 g vs. -0.23 ± 0.14 g, adjusted $p = 0.037$), a higher loss of total femur (-0.18 ± 0.08 g/cm^2 vs. -0.14 ± 0.08 g/cm^2, $p = 0.008$) and whole-body bone mineral density (-0.14 ± 0.07 g/cm^2 vs. -0.10 ± 0.13 g/cm^2, $p = 0.074$). Postmenopausal patients presented a greater decrease in total body lean mass (-7.52 ± 3.06 kg vs. -7.27 ± 3.22 kg, $p = 0.014$) and arms lean mass (-1.00 ± 1.16 kg vs. -0.68 ± 0.90 kg, $p = 0.020$).

Conclusion This study demonstrates that, although weight loss is comparable between groups, postmenopausal women undergoing MBS experience a more significant loss of lean mass and bone mineral density. These findings underscore the need for tailored post-surgical strategies, including optimized nutritional support and vigilant bone health monitoring, to mitigate potential adverse effects in this population.

Highlights

- Metabolic-Bariatric Surgery (MBS) is the primary approach for severe obesity but may have potential adverse effects on the skeletal system.
- Postmenopausal women undergoing MBS experience a greater loss of lean mass and bone mineral density.
- These findings underscore the necessity for tailored post-surgical strategies.

Keywords Metabolic-bariatric surgery · Menopause · Body composition · Bone metabolism · Sarcopenic obesity · Cardiometabolic outcomes

Mafalda Maia and Fernando Mendonça contributed equally to this work.

Extended author information available on the last page of the article

Published online: 17 March 2026

Introduction

The prevention and treatment of obesity epidemic have remained a longstanding challenge. This disease is widely recognized as a major global health issue due to its association with a broad spectrum of comorbidities, including cardiovascular diseases, type 2 diabetes mellitus (T2D), and certain types of cancer, all of which can lead to premature disability and death [1]. Over the last decades, obesity prevalence has increased dramatically. According to the World Health Organization, in 2022, approximately 2.5 billion adults were overweight or had obesity (43%), including over 890 million adults living with obesity (16%) [2].

Metabolic-Bariatric surgery (MBS) has become a central treatment for severe obesity, providing substantial improvements in weight loss and resolution of obesity-related comorbidities such as sarcopenic obesity (SO) [3]. This condition is characterized by the combination of muscle deterioration and high adiposity and is associated with a wide range of important comorbidities. Studies suggest that the management of SO should embrace both lifestyle and medical therapies, and MBS unfolds as the second-line option for patients with class II or III obesity who meet the criteria [4].

Despite the well-documented benefits of MBS, its potential adverse effects on the skeletal system are still a concern, particularly regarding its impact on bone loss [5]. These effects are attributed to multiple factors, including impaired calcium intake and absorption, secondary hyperparathyroidism resulting from reduced vitamin D absorption, and alterations in gastrointestinal and adipocyte hormone profiles [6, 7]. MBS, particularly hypoabsorptive procedures, appears to exacerbate bone loss, with fractures emerging as the most clinically significant outcome. These fractures not only undermine skeletal integrity but also lead to heightened morbidity and mortality [8].

Given that women constitute most of the patients undergoing MBS, menopausal status, as well as age, may emerge as critical determinants of surgical effectiveness. The transition from pre- to post-reproductive life changes the adipose tissue metabolism, reducing lipoprotein lipase activity and impairing lipolysis, which contributes to lean mass loss and increases total and visceral adipose tissue [9]. Additionally, changes in reproductive hormones and body composition during the menopausal transition contribute to an elevated risk of metabolic and cardiovascular diseases, including hypertension (HTN), dyslipidaemia, and obesity [10].

However, there is a lack of studies addressing the impact of age and menopausal status on MBS-induced changes on cardiometabolic profile, bone metabolism, and body composition. Considering the pivotal role of menopause in bone health, which directly impacts patient morbidity, it is crucial to further investigate its impact on outcomes following MBS.

Therefore, this study aims to clarify the associations between menopause at the time of surgery and changes in cardiometabolic risk factors, bone mineral density, and body composition, as well as to study the relevance of SO in women within a 24-month follow-up period after MBS.

Materials and Methods

Subjects and Study Design

This prospective single-center study followed 162 female patients with obesity who were consecutively selected and submitted to MBS during the preoperative evaluation by the Integrated Responsibility Center for Obesity (CRIO) between November/2019 and December/2022.

The eligibility criteria for this study were as follows:

a) Women ≥ 40 years-old;
b) Body Mass Index (BMI) ≥ 35 kg/m² with at least one comorbidity (e.g., metabolic syndrome, T2D, dyslipidemia, HTN, cardiorespiratory disease, among others) or BMI ≥ 40 kg/m² regardless of comorbidities;
c) Obesity non-secondary to classical endocrine disease;
d) At least one year of non-surgical appropriate measures without achieving satisfactory weight loss;
e) Undergoing either Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG);
f) Follow-up for at least 12 months after MBS;
g) Presenting pre and at least one post-operative Dual-Energy X-ray Absorptiometry (DXA) evaluation.

The exclusion criteria included:

a) Evaluation for a second metabolic-bariatric or revisional surgery;
b) Weight over 140 kg, which is the maximum capacity supported by the DXA equipment;
c) Unstable psychiatric disorders or substance dependency (narcotics or alcohol);
d) Hyperthyroidism;
e) Hypercalcemia (corrected calcium > 10.2 mg/dL);
f) Glomerular filtration rate ≤ 30mL/min/1.73 m²;
g) Diseases affecting bone metabolism (e.g., primary hyperparathyroidism, Paget's disease of bone, osteoporosis);
h) History of intestinal malabsorption (e.g., celiac disease, short bowel syndrome, previous intestinal disease);

i) Critical medical condition, such as cardiovascular, pulmonary, hepatic, renal, osteoarticular diseases, or malignant neoplasms;
j) Therapy with thiazolidinediones or canagliflozin;
k) Previous or current anti-osteoporotic therapy (e.g., bisphosphonates, teriparatide, raloxifene, denosumab);
l) Prior (within the past year) or current systemic therapy with corticosteroids or estrogens as hormone replacement therapy.

Multivitamin supplements were prescribed to all patients, with specific supplements (such as vitamin D and, less commonly, calcium carbonate) being added in a case-by-case basis. Vitamin D supplements were either cholecalciferol pills (between 22,400 and 30,000 international units each pill), cholecalciferol oral solution (0.5 mg/ml, 667 international units each droplet), or calcifediol pills (0.266 mg each pill). They were prescribed and adjusted according to the severity of vitamin D deficiency (at least 3000 IU/day and up to 6000 IU/day of cholecalciferol). Calcium carbonate supplements (1500 mg per day) were added as an add-on to vitamin D supplements in some cases of secondary hyperparathyroidism, based on calcium corrected for albumin levels.

The study was carried out in accordance with the protocol approved by the Ethics Committee of our hospital Centre (reference no. 276/2018). All procedures were performed in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki, and relevant national laws. The surgical team selected the surgery technique based on the best clinical practices.

Pre- and Post-Operative Assessments

Clinical and analytical evaluations were performed prior to surgery and at 6, 12, and 24 months following MBS. Menopause was defined as 12 consecutive months without menstruation, with no other obvious physiological or pathological cause, and in the absence of clinical intervention [11]. Menopausal status was defined at baseline (time of surgery) and used as the grouping variable for all longitudinal analyses. Participants were not reclassified during follow-up, and menopausal transition was not modelled as a time-varying exposure. Osteopenia and osteoporosis were defined according to World Health Organization (WHO) criteria based on DXA T-scores, with osteopenia defined as a T-score between − 1.0 and − 2.5 and osteoporosis defined as a T-score ≤ − 2.5.

Information regarding personal history and comorbidities, medications and supplements taken before and after surgery, menopausal status, as well as lifestyle habits such as tobacco and alcohol use, was gathered from medical records.

The presence of comorbidities, including HTN, T2D, and dyslipidemia were investigated, both at baseline and after a 24-month follow-up period. HTN was characterized by an office-based systolic blood pressure (SBP) ≥140mmHg and/or a diastolic blood pressure (DBP) ≥90mmHg in at least one visit, or the use of antihypertensive medication. Blood pressure was evaluated with the patient seated for a minimum of 5 min during Endocrinology consultations.

T2D was diagnosed with a fasting glucose (FG) level ≥ 126 mg/dL, a glycated hemoglobin (HbA1c) level ≥ 6.5%, or the use of antidiabetic medication. Dyslipidemia was defined by low-density lipoprotein cholesterol (LDL) ≥130 mg/dL, high-density lipoprotein cholesterol (HDL) ≤50 mg/dL, triglycerides (TG) ≥150 mg/dL, total cholesterol (TC) ≥240 mg/dL, or the use of statin or fibrate therapy.

Remission of any of these comorbidities during the follow-up period was characterized by a participant who had been diagnosed with a comorbidity prior to surgery but no longer satisfied the diagnostic criteria one or two years following MBS.

Anthropometric measurements were conducted, including body weight (BW), height (H), waist circumference, and BMI, which was calculated by dividing weight in kilograms by height in meters squared.

Blood samples were collected after a minimum 12-hour fast. The biochemical parameters assessed included albumin, total proteins, TC, LDL, HDL, TG, vitamin D, vitamin B12, folic acid, magnesium (Mg), total calcium corrected for albumin levels, phosphorus (P+), FG, insulin, C-peptide, HbA1c, parathyroid hormone (PTH), osteocalcin, C-terminal telopeptide (CTX), thyroid-stimulating hormone (TSH), free thyroxine (FT4) and urinary albumin-to-creatinine ration. The estimated glomerular filtration rate (eGFR) was determined for all participants using the CKD-EPI formula [12].

Dual-Energy X-ray Absorptiometry was employed to evaluate body composition, using a properly calibrated densitometer (Lunar iDXA model), and was performed before, and 1 and 2 years after MBS. The analyzed parameters included bone mineral density, T-score, and Z-score at the lumbar spine (L1-L4), total femur, femoral neck, and full body. Other evaluated parameters included total body fat (kg), total fat mass percentage, trunk and leg fat mass percentage, lean mass of the arms and legs, and bone mineral content (BMC). Sarcopenic obesity was assessed based on the total lean mass of the arms and legs (appendicular lean mass, ALM) relative to body weight (W), following the consensus guidelines for caucasian women aged 18–65 years, which define a threshold of ALM/W < 23.47% [13].

Statistical Analysis

Results are presented as mean ± standard deviation for continuous normally distributed variables, or as median (Minimum, Maximum) for non-normally distributed continuous variables. Categorical variables are presented as count and percentages.

The differences in parameters between baseline and 6, 12, and 24 months were used for group comparisons. Participants were divided into two groups based on the presence of menopause at the time of surgery.

Clinical, analytical, and DXA parameters at baseline, as well as their variations between baseline and 6, 12, and 24 months, were compared according to the menopause status using t-student tests for parametric variables, Mann-Whitney U tests, for non-parametric variables, and $\chi 2$ tests for categorical variables. These comparisons were adjusted for age, type of MBS and baseline BMI using multivariable regression models in which each postoperative clinical, analytical, and densitometric parameters (or its change from baseline) was entered as a dependent variable, and menopausal status was included as independent variable.

In a secondary analysis, we explored whether the observed DXA changes were driven by baseline skeletal status by (i) additionally adjusting the linear regression models evaluating DXA parameters for the presence of osteopenia at baseline, and (ii) comparing densitometric parameters according to baseline osteopenia status using Student's t tests, Mann–Whitney U tests, and χ^2 tests, as appropriate.

A subgroup analysis of analytical and DXA parameter changes at 12 and 24 months after surgery was also performed, including only patients who underwent RYGB.

Reported p- values are two-tailed and $p \leq 0.05$ was considered statistically significant. Analyses were conducted with the use of STATA 18.0® software.

Results

Baseline Clinical Characteristics of the Overall Study Sample and According to the Menopausal Status

This study included a total of 162 female participants, 82 premenopausal and 80 postmenopausal, with a mean age of 50.8 years, a mean weight of 108.2 kg and a mean BMI of 42.1 kg/m^2. Most patients underwent RYGB (99, 61.1%), while 63 (38.9%) underwent SG. The prevalence of SO in the overall sample was 89.5% at the time of surgery. The baseline characteristics of the overall sample, as well as those of the two groups, are presented in Table 1.

Table 1 Baseline characteristics of the overall sample and comparison among participants categorized by the menopausal status

Variable	Baseline			
	Overall	No Menopause (n=82)	Menopause (n=80)	P Value
Age*	50.8±7.3	45.7±4.6	56.0±5.8	**<0.001**
Surgical Procedure				0.35
RYGB, n (%)	99 (61.1)	53 (64.6)	46 (57.5)	
SG, n (%)	63 (38.9)	29 (35.4)	34 (42.5)	
Weight (kg)*	108.2±13.5	109.2±14.3	107.3±12.5	0.35
BMI (kg/m2)*	42.1±4.7	42.3±4.9	41.9±4.4	0.60
Waist Circumference (cm)*	118.8±10.4	**115.5±11.3**	**121.5±8.9**	**0.024**
Hip Circumference (cm)*	129.0±9.0	130.4±8.9	127.8±9.0	0.28
SBP (mmHg)*	140.7±15.5	**137.0±14.5**	**144.2±15.7**	**0.021**
DBP (mmHg)*	86.0±10.7	84.1±11.2	88.0±9.9	0.08
DM2, n (%)	52 (32.7)	**17 (21.2)**	**35 (44.3)**	**0.002**
HTN, n (%)	114 (87.7)	**51 (81.0)**	**63 (94.0)**	**0.023**
Dyslipidemia, n (%)	128 (81.0)	61 (77.2)	67 (84.8)	0.22
Osteopenia, n (%)	34 (21.0)	**11 (13.4)**	**23 (28.7)**	**0.017**
Sarcopenic Obesity, n (%)	145 (89.5)	73 (89.0)	72 (90.0)	0.84
FSH (mUI/mL)**	17.4 [6.0,44.9]	**6.6 [4.2, 9.3]**	**44.3 [32.5, 61.3]**	**<0.001**
LH (mUI/mL)**	17.9 [5.0,31.4]	**5.5 [3.9, 9.7]**	**30.2 [21.1, 38.9]**	**<0.001**
CKD stage 1 to 3	27 (16.6)	14.2 (17.3)	12.7 (15.9)	0.81

Data in this table are either expressed as *mean ± SD or as **median [25-75th percentile]. Abbreviations: BMI body mass index, RYGB roux-en-Y gastric bypass, SG vertical sleeve gastrectomy, SBP systolic blood pressure, DBP diastolic blood pressure, DM2 type 2 diabetes mellitus, HTN hypertension, FSH follicle stimulating hormone, LH luteinizing hormone, CKD chronic kidney disease

There were no differences between groups at baseline regarding weight and BMI. However, postmenopausal patients showed a higher waist circumference (121.5 ± 8.9 vs. 115.5 ± 11.3 cm, p = 0.024). Regarding comorbidities, a greater proportion of patients after menopause presented T2D (44.3 vs. 21.2%, p=0.002) and HTN (94.0 vs. 81.0%, p=0.023). On the other hand, no differences were found between the groups concerning dyslipidemia's prevalence. Osteopenia was more prevalent among postmenopausal individuals (28.7 vs. 13.4%, p=0.017), whereas there were no differences among groups regarding SO. Multivitamin and mineral supplementation was similar at baseline between groups (Supplementary Table 1).

Concerning DXA results at baseline, we found that postmenopausal women had lower BMC (2.52 ± 0.32 vs. 2.66 ± 0.31 g, p = 0.004), legs lean mass (17.0 ± 2.4 vs. 17.8 ± 2.7 kg, p=0.043), lumber spine Z-score (0.25 [-0.5, 1.1] vs. -0.35 [-0.9, 0.6], p=0.010), femoral neck bone mineral

Table 2 Comparative analysis of body composition assessed by DXA and laboratory parameters at baseline, and variation one and two-years after MBS

Variable	Baseline			Variation one-year after MBS				Variation two-years after MBS			
	No Menopause ($n=82$)	Menopause ($n=80$)	*P* Value	No Menopause ($n=78$)	Menopause ($n=78$)	*P* Value	Adjusted *P* Value	No Menopause ($n=66$)	Menopause ($n=64$)	*P* Value	Adjusted *P* Value
BMC (g)	**2.66 ± 0.31**	**2.52 ± 0.32**	**0.004**	-0.17 ± 0.11	-0.16 ± 0.14	0.60	0.80	**-0.23 ± 0.14**	**-0.31 ± 0.13**	**0.001**	**0.001**
Total Body Mass (kg)	107.2 ± 14.0	105.6 ± 12.2	0.42	-36.8 ± 10.0	-35.5 ± 10.2	0.42	**0.03**	-38.6 ± 12.1	-37.7 ± 10.5	0.65	0.05
Total Body Fat (%)	51.9 ± 3.8	52.1 ± 3.1	0.77	-17.7 ± 6.3	-15.9 ± 6.7	0.09	0.75	-16.8 ± 6.8	-16.3 ± 7.2	0.71	0.37
Body Lean Mass (kg)	50.1 ± 5.9	49.3 ± 5.7	0.37	-6.04 ± 3.29	-6.49 ± 2.98	0.37	**0.033**	**-7.27 ± 3.22**	**-7.52 ± 3.06**	0.66	**< 0.001**
Arms Lean Mass (kg)	5.37 ± 1.10	5.65 ± 1.28	0.14	**-0.54 ± 0.85**	**-0.92 ± 1.13**	**0.020**	**0.001**	**-0.68 ± 0.90**	**-1.00 ± 1.16**	0.08	**0.015**
Legs Lean Mass (kg)	**17.8 ± 2.7**	**17.0 ± 2.4**	**0.043**	-3.25 ± 1.50	-3.25 ± 1.47	0.98	0.13	-3.78 ± 1.58	-3.79 ± 1.44	0.97	0.05
L1-L4 BMD (g/cm^2)	**1.26 ± 0.14**	**1.22 ± 0.16**	**0.070**	-0.05 ± 0.06	-0.06 ± 0.07	0.32	0.77	-0.08 ± 0.08	-0.11 ± 0.09	0.07	0.10
L1-L4 T-score	**0.50 [-0.2, 1.3]**	**0.15 [-0.8, 1.0]**	**0.050**	-0.40 ± 0.49	-0.47 ± 0.59	0.40	0.95	-0.63 ± 0.63	-0.84 ± 0.70	0.07	0.18
Femoral Neck BMD (g/cm^2)	**1.07 ± 0.13**	**1.00 ± 0.13**	**< 0.001**	-0.08 ± 0.06	-0.08 ± 0.07	0.76	0.70	-0.11 ± 0.08	-0.12 ± 0.07	0.79	0.42
Femoral Neck T-score	**0.75 [0.0,1.5]**	**0.15 [-0.7,1.0]**	**< 0.001**	-0.68 ± 0.52	-0.65 ± 0.61	0.76	0.85	-0.92 ± 0.63	-0.96 ± 0.62	0.75	0.43
Total Femur BMD (g/cm^2)	1.20 ± 0.12	1.16 ± 0.15	0.07	-0.10 ± 0.06	-0.12 ± 0.06	0.06	**0.008**	**-0.14 ± 0.08**	**-0.18 ± 0.08**	**0.003**	**< 0.001**
Total Femur T-score	1.65 [1.0,2.4]	1.40 [0.4,2.0]	0.06	-0.87 ± 0.48	-1.00 ± 0.50	0.10	**0.020**	**-1.18 ± 0.63**	**-1.52 ± 0.66**	**0.003**	**< 0.001**
Total Body BMD (g/cm^2)	**1.27 ± 0.10**	**1.23 ± 0.11**	**0.004**	-0.04 ± 0.05	-0.06 ± 0.05	0.06	0.24	**-0.10 ± 0.13**	**-0.14 ± 0.07**	**0.031**	**0.04**
Total Body T-score	**2.10 [1.5,2.8]**	**1.55 [0.9,2.4]**	**0.004**	**-0.43 ± 0.49**	**-0.60 ± 0.51**	**0.043**	0.18	**-0.84 ± 0.56**	**-1.38 ± 0.64**	**< 0.001**	**< 0.001**
Hip FRAX	**1.00 [0.9,1.3]**	**2.00 [1.4,3.0]**	**< 0.001**	0.07 ± 0.16	0.20 ± 0.82	0.17	0.27	**0.13 ± 0.29**	**0.34 ± 1.04**	0.13	0.54
Major FRAX	**0.00 [0.0,0.1]**	**0.10 [0.0,0.3]**	**< 0.001**	**0.34 ± 0.32**	**1.05 ± 1.26**	**< 0.001**	0.27	**0.38 ± 0.62**	**1.48 ± 1.63**	**< 0.001**	0.85

Data in this table are either expressed as mean ± SD or as median [25-75th percentile]. Adjusted P-values were obtained from multivariable linear and logistic regression analysis considering postoperative clinical, analytical, and densitometric parameters (or its change from baseline) as dependent variables and menopausal status as independent variable, adjusted for age, baseline BMI and type of surgery. Abbreviations: BMI, body mass index; BMC bone mineral content, L1-L4 lumbar spine from 1 to 4, BMD bone mineral density, MBS metabolic-bariatric surgery

density (BMD) (1.00 ± 0.13 vs. 1.07 ± 0.13 g/cm^2, $p<0.001$) and femoral neck T-score (0.15 [-0.7,1.0] vs. 0.75 [0.0,1.5], $p<0.001$), total body BMD (1.23 ± 0.11 vs. 1.27 ± 0.10 g/cm^2, $p=0.004$) and total body T-score (1.55 [0.9,2.4] vs. 2.10 [1.5,2.8], $p=0.004$) (Table 2).

With respect to phospho-calcium parameters at baseline (Table 3), PTH (58.5 ± 23.2 vs. 51.6 ± 17.6pg/mL, $p=0.036$) and P+ levels (3.46 ± 0.52 vs. 3.26 ± 0.47 mg/dL, $p=0.015$) were higher in postmenopausal women although there were no differences neither in vitamin D nor in total corrected calcium. Levels of beta-crosslaps (CTX) were higher in the postmenopausal group (0.34 ± 0.17 vs. 0.28 ± 0.12pg/mL, $p=0.022$) in the baseline, with higher osteocalcin levels, however not statistically significant (15.8 ± 4.9 vs. 17.5 ± 6.1ng/mL, $p=0.07$). Postmenopausal group exhibited higher levels of TC (195.1 ± 51.5 vs. 183.4 ± 34.2 mg/dL, $p=0.09$) and HDL (52.2 ± 12.4 vs. 49.1 ± 9.1 mg/dL, $p=0.07$), as well as higher levels of FG (119.9 ± 40.6 vs. 103.6 ± 23.7 mg/dL, $p=0.002$) and HbA1c (6.16 ± 1.06 vs. 5.74 ± 0.68%, $p=0.003$) (Table 4).

Post-MBS Variation in Clinical and Analytical Parameters According to Menopausal Status

There were no differences between groups regarding BMI variation after surgery. Notably, two years after MBS, postmenopausal patients showed higher reduction of HbA1C (-0.67 ± 0.86 vs. -0.12 ± 2.61%, $p=0.08$) than premenopausal patients, however not reaching statistical significance. Regarding comorbidities remission, no differences

Table 3 Comparative analysis of laboratory phospho-calcium parameters and bone markers at baseline, and their variation one and two-years after MBS

Variable	Baseline			Variation one-year after MBS				Variation two-years after MBS			
	No Menopause (n=82)	Menopause (n=80)	P Value	No Menopause (n=78)	Menopause (n=78)	P Value	Adjusted P Value	No Menopause (n=66)	Menopause (n=64)	P Value	Adjusted P Value
Total Ca corrected for albumin (mEq/L)	9.31 ± 0.30	9.40 ± 0.31	0.08	**0.07 ± 0.37**	**0.25 ± 0.63**	**0.025**	0.26	**-0.08 ± 0.65**	**0.14 ± 0.36**	**0.018**	**0.014**
P+ (mg/dL)	**3.26 ± 0.47**	**3.46 ± 0.52**	**0.015**	0.47 ± 0.47	0.56 ± 0.62	0.34	0.14	0.33 ± 0.66	0.50 ± 0.58	0.13	0.05
Mg (mEq/L)	1.59 ± 0.11	1.57 ± 0.14	0.44	0.03 ± 0.11	0.02 ± 0.13	0.65	0.35	0.59 ± 4.62	0.03 ± 0.12	0.33	0.06
Vitamin D (ng/mL)	18.0 [13.0, 22.0]	19.0 [14.0, 23.0]	0.56	**7.48 ± 12.2**	**12.2 ± 13.4**	**0.023**	**0.013**	8.73 ± 13.9	12.0 ± 12.68	0.15	0.91
Vitamin D deficit, n (%)	70 (88.6)	71 (89.9)	0.80	**54 (65.9)**	**36 (46.2)**	**0.012**	**0.040**	**47 (64.4)**	**30 (44.7)**	**0.020**	0.20
PTH (pg/mL)	**51.6 ± 17.6**	**58.5 ± 23.2**	**0.036**	**0.93 ± 17.3**	**-8.67 ± 22.4**	**0.003**	0.06	**10.2 ± 24.5**	**0.61 ± 26.23**	**0.030**	0.20
PTH > 65pg/mL (%)	**18 (22.8)**	**27 (35.5)**	**0.08**	**18 (22.0)**	**15 (18.8)**	**0.61**	0.14	**25 (34.3)**	**23 (34.3)**	**0.99**	0.54
CTX (pg/mL)	**0.28 ± 0.12**	**0.34 ± 0.17**	**0.022**	**0.48 ± 0.21**	**0.64 ± 0.27**	**< 0.001**	**0.005**	0.48 ± 0.96	0.57 ± 0.28	0.50	0.77
Osteocalcin (ng/mL)	15.8 ± 4.9	17.5 ± 6.1	0.07	**18.8 ± 11.1**	**24.5 ± 13.7**	**0.008**	0.08	**18.6 ± 11.0**	**29.0 ± 17.2**	**<0.001**	**<0.001**
24 H-Urine Ca (mg/kg/24 h)	7.10 [4.4,10.4]	7.80 [4.8,10.6]	0.99	**-2.52 ± 4.87**	**0.07 ± 4.06**	**0.001**	**0.04**	-1.65 ± 4.68	-0.32 ± 3.93	0.11	0.64

Data in this table are either expressed as mean ± SD or as median [25-75th percentile]. Adjusted P-values were obtained from multivariable linear and logistic regression analysis considering postoperative clinical, analytical, and densitometric parameters (or its change from baseline) as dependent variables and menopausal status as independent variable, adjusted for age, baseline BMI and type of surgery. Abbreviations: MBS metabolic-bariatric surgery, P+ phosphorus, Ca calcium, Mg magnesium, PTH parathyroid hormone, CTX C-terminal telopeptide

were found between groups two years after MBS, with the same occurring with the variation of SBP, DBP and lipid profile parameters (Table 4).

Following MBS, post-menopausal women presented a lower prevalence of vitamin D deficit in the first year (46.2 vs. 65.9%, p = 0.054), and a greater increase, not statistically significant, in albumin-corrected calcium levels two years after MBS (0.14 ± 0.36 vs. -0.08 ± 0.65mEq/L, p = 0.059). No significant differences were observed in the other phospho-calcium metabolism parameters 2 years after MBS. Furthermore, no differences in vitamin D or calcium supplementation were observed between groups (Supplementary Table 1). There were no statistically significant differences in PTH levels regarding vitamin D deficiency status at one (50.3 ± 20.6 vs. 51.2 ± 14.7pg/mL, p = 0.77) and 2 years (56.1 ± 21.6 vs. 63.1 ± 27.2pg/mL, p = 0.10) after MBS, the same occurring with surgery type (SG vs. RYGB 1 year after surgery: 48.5 ± 16.0 vs. 52.8 ± 18.5pg/mL, p = 0.13, two years after: 61.9 ± 22.0 vs. 58.9 ± 26.4pg/mL, p = 0.51). It is also important to mention that prevalence of patients with 1 to 3 CKD stages at baseline (considering the baseline levels of creatinine and microalbuminuria) was similar between groups (15.9% vs. 17.3%, p = 0.81).

Levels of CTX and osteocalcin showed greater increases at 6 months among post-menopausal women (Supplementary Table 2), and this was also observed with CTX 1 year and osteocalcin 2 years after MBS (Table 3).

Post-MBS Variations in Densitometric Parameters Assessed by DXA According to Menopausal Status

Osteopenia was more prevalent among postmenopausal individuals one (48.7 vs. 26.0%, p = 0.003) and two years after surgery (56.3 vs. 34.9%, p = 0.014), however, this association did not remain statistically significant after adjustment for age, baseline BMI, type of surgery and osteopenia at baseline. No differences were observed between groups regarding either SO or osteoporosis (Table 5).

Among patients with normal BMD at baseline (n = 128), 33 (32.4%) progressed to osteopenia at 2 years. Among those with baseline osteopenia (n = 34), 9 (28.1%) progressed to osteoporosis. Patients with normal baseline BMD showed a greater reduction in femoral neck BMD at 1 and 2 years, whereas the remaining BMD parameters did not differ significantly according to baseline skeletal status (Supplementary Table 3). Variations in densitometric parameters assessed by DXA according to menopausal status are presented in Table 2 and Supplementary Table 4. Postmenopausal patients exhibited a steeper decrease in BMC two years after MBS (-0.31 ± 0.13 vs. -0.23 ± 0.14 g, p = 0.037). Postmenopausal women also showed a higher loss of total femur BMD (-0.18 ± 0.08 vs. -0.14 ± 0.08 g/cm^2, p = 0.008), T-score (-1.52 ± 0.66 vs. -1.18 ± 0.63, p = 0.008) and Z-score (-0.65 ± 0.59 vs. -0.39 ± 0.64, p = 0.025), and total body BMD (-0.14 ± 0.07 vs. -0.10 ± 0.13 g/cm^2, p = 0.074),

Table 4 Comparative analysis of analytical parameters at baseline, and variation one and two-years after MBS

Variable	Baseline			Variation one-year after MBS				Variation two-years after MBS			
	No Menopause ($n=82$)	Menopause ($n=80$)	*P* Value	No Menopause ($n=81$)	Menopause ($n=79$)	*P* Value	Adjusted *P* Value	No Menopause ($n=71$)	Menopause ($n=67$)	*P* Value	Adjusted *P* Value
Hemoglobin (g/dL)	**13.4 ± 1.0**	**13.7 ± 0.9**	**0.039**	-0.45 ± 1.1	-0.63 ± 1.0	0.27	0.53	-0.54 ± 1.03	-0.59 ± 1.00	0.75	0.22
TC (mg/dL)	183.4 ± 34.2	195.1 ± 51.5	0.09	-22.1 ± 32.0	-19.1 ± 45.5	0.63	0.87	-17.4 ± 34.4	-11.1 ± 58.1	0.44	0.24
HDL (mg/dL)	49.1 ± 9.1	52.2 ± 12.4	0.07	5.87 ± 8.22	4.01 ± 8.11	0.15	0.07	10.6 ± 9.6	10.8 ± 10.2	0.88	0.70
LDL (mg/dL)	110.6 ± 30.1	116.8 ± 39.0	0.26	-20.1 ± 25.9	-15.5 ± 38.4	0.38	0.57	-18.9 ± 30.6	-14.3 ± 46.5	0.49	0.33
TG (mg/dL)	108.5 [83.0, 146.0]	109.0 [88.0, 166.0]	0.34	-46.4 ± 72.2	-38.2 ± 47.9	0.40	0.11	-51.1 ± 86.3	-39.5 ± 56.1	0.36	0.24
FG (mg/dL)	**103.6 ± 23.7**	**119.9 ± 40.6**	**0.002**	**-12.8 ± 27.4**	**-24.8 ± 45.0**	**0.043**	**0.007**	-22.8 ± 27.8	-33.1 ± 38.7	0.07	0.10
HbA1C (%)	**5.74 ± 0.68**	**6.16 ± 1.06**	**0.003**	**-0.46 ± 0.48**	**-0.71 ± 0.90**	**0.028**	0.10	-0.12 ± 2.61	-0.67 ± 0.86	0.11	0.02
Insulin (µU/mL)	17.9 [13.2, 25.2]	20.9 [14.1, 26.5]	0.28	**-14.7 ± 24.5**	**-15.8 ± 20.2**	0.78	**0.030**	-16.8 ± 23.9	-16.9 ± 20.9	0.99	0.17
C-Peptide (ng/mL)	3.95 ± 1.56	4.31 ± 1.93	0.21	-1.87 ± 1.49	-1.99 ± 1.95	0.64	0.18	-1.83 ± 2.03	-2.18 ± 1.83	0.31	0.14
TSH (µUI/mL)	1.52 [1.1, 2.2]	1.54 [1.2,2.2]	0.61	-0.27 ± 0.66	-0.34 ± 1.65	0.73	0.78	-0.28 ± 0.69	-0.16 ± 0.65	0.28	0.40
T4L (ng/dL)	0.94 ± 0.10	0.97 ± 0.12	0.12	0.04 ± 0.11	0.04 ± 0.11	0.64	0.91	0.05 ± 0.11	0.05 ± 0.12	0.95	0.81
AST (U/L)	**20.0 [16.0, 24.0]**	**21.0 [19.0, 27.5]**	**0.006**	1.53 ± 9.36	3.57 ± 19.00	0.40	0.63	1.83 ± 9.34	2.00 ± 13.95	0.93	0.49
ALT (U/L)	**20.0 [16.0, 27.5]**	**24.0 [18.0, 30.0]**	**0.017**	-0.04 ± 12.71	3.50 ± 32.59	0.37	0.81	-0.49 ± 14.18	1.23 ± 20.62	0.57	0.88
GGT (U/L)	**24.0 [16.0, 35.0]**	**30.0 [20.0, 42.0]**	**0.025**	-11.4 ± 12.4	-18.7 ± 79.7	0.43	0.57	-6.93 ± 26.82	-14.6 ± 102.4	0.55	0.44
ALP (U/L)	**76.3 ± 16.6**	**85.4 ± 24.8**	**0.008**	-2.65 ± 16.55	-0.73 ± 22.13	0.54	0.46	-3.89 ± 20.03	2.16 ± 24.83	0.12	0.60
Uric Acid (mg/dL)	5.20 ± 1.30	5.50 ± 1.30	0.18	-1.18 ± 1.00	-1.20 ± 1.08	0.93	0.61	-1.23 ± 0.99	-1.20 ± 1.24	0.85	0.53
Creatinine (mg/dL)	0.64 ± 0.12	0.66 ± 0.17	0.60	0.00 ± 0.09	-0.00 ± 0.14	0.70	0.86	0.04 ± 0.40	0.04 ± 0.55	0.95	0.18
eGFR (mL/min/1.73 m^2)	**106.5 ± 11.2**	**98.4 ± 14.4**	**< 0.001**	-0.89 ± 8.80	-0.23 ± 10.91	0.67	0.80	-2.07 ± 13.16	-0.49 ± 14.89	0.51	0.15
Albumin-to-creatinine ratio (mg/g)	7.15 [4.0,20.9]	6.75 [4.0,13.4]	0.63	-31.0 ± 128.7	-17.8 ± 145.1	0.55	0.49	-23.1 ± 83.0	-5.8 ± 190.4	0.49	0.52
Biliary Acids (mg/dL)	2.10 [1.2,3.2]	2.40 [1.6,3.7]	0.20	1.35 ± 3.65	0.49 ± 5.13	0.24	0.58	1.22 ± 3.92	1.43 ± 4.55	0.78	0.50

Data in this table are either expressed as mean ± SD or as median [25-75th percentile]. Adjusted P-values were obtained from multivariable linear and logistic regression analysis considering postoperative clinical, analytical, and densitometric parameters (or its change from baseline) as dependent variables and menopausal status as independent variable, adjusted for age, baseline BMI and type of surgery. Abbreviations: FG fasting glucose, HbA1c hemoglobin A1c, CT total cholesterol, HDL high-density lipoprotein cholesterol, LDL low-density lipoprotein cholesterol, TG triglycerides, T4L free thyroxine, TSH thyroid-stimulating hormone, GGT gamma-glutamyltransferase, ALP alkaline phosphatase, AST aspartate aminotransferase, ALT alanine aminotransferase, GFR glomerular filtration rate

T-score (-1.38 ± 0.64 vs. -0.84 ± 0.56, $p = 0.010$) and Z-score (-0.01 ± 0.68 vs. 0.46 ± 0.67, $p = 0.09$) two years after MBS. Variations in femoral neck and lumbar spine BMD were not significantly different between groups. These data are supported by a multivariable linear regression analysis of the association between menopausal status and densitometric outcomes (Supplementary Table 5). The absolute values of all variables are displayed in Supplementary Table 6). Furthermore, postmenopausal patients presented a slightly greater decrease in total body lean mass (-7.52 ± 3.06 vs. -7.27 ± 3.22 kg, $p = 0.014$) and arms lean mass (-1.00 ± 1.16 vs. -0.68 ± 0.90 kg, $p = 0.020$) two years after MBS, which was also evident one year after surgery. Although statistically significant, the absolute difference between groups was small (-0.3 kg).

The analysis of densitometric and analytical parameters including only patients who had undergone RYGB showed results similar to those previously reported (Supplementary Tables 7 and 8).

The authors found no association between postmenopausal status and the development of osteopenia or osteoporosis after MBS at either 1 or 2 years (Supplementary Table 9).

Table 5 Comparative analysis of prevalence of comorbidities, anthropometric parameters, blood pressure at baseline, and variation one and two-years after MBS

Variable	Baseline			Variation one-year after MBS				Variation two-years after MBS			
	No Menopause ($n=82$)	Menopause ($n=80$)	*P* Value	No Menopause ($n=81$)	Menopause ($n=79$)	*P* Value	Adjusted *P* Value	No Menopause ($n=71$)	Menopause ($n=67$)	*P* Value	Adjusted *P* Value
Weight (kg)	109.2 ± 14.3	107.3 ± 12.5	0.35	**-38.7 ± 10.2**	**-36.7 ± 10.3**	0.23	**0.009**	-40.5 ± 12.3	-38.8 ± 11.7	0.41	0.19
BMI (kg/m^2)	42.3 ± 4.9	41.9 ± 4.4	0.60	-15.0 ± 3.9	-14.4 ± 4.1	0.36	**0.040**	-15.6 ± 4.7	-15.2 ± 4.8	0.60	0.37
SBP (mmHg)	**137.0 ± 14.5**	**144.2 ± 15.7**	**0.021**	-16.3 ± 20.8	-12.1 ± 22.3	0.50	0.51	-8.58 ± 14.9	-14.5 ± 25.8	0.40	0.65
DBP (mmHg)	84.1 ± 11.2	88.0 ± 9.9	0.08	-12.9 ± 17.2	-17.2 ± 16.0	0.37	0.45	-12.6 ± 13.1	-12.5 ± 17.3	0.98	0.85
DM2 Remission, n (%)	-	-	-	10 (58.8)	22 (62.9)	0.78	0.84	12 (85.7)	21 (77.8)	0.54	0.70
HTN Remission, n (%)	-	-	-	14 (43.8)	16 (32.7)	0.31	0.63	9 (33.3)	9 (27.3)	0.61	0.46
Dyslipidemia Remission, n (%)	-	-	-	28 (45.9)	24 (35.8)	0.25	0.76	32 (60.4)	29 (53.7)	0.49	0.58
Osteopenia, n (%)*	**11 (13.4)**	**23 (28.7)**	**0.017**	**20 (26.0)**	**36 (46.2)**	**0.009**	0.75	**22 (32.8)**	**33 (49.3)**	**0.05**	0.59
Sarcopenic Obesity, n (%)*	73 (89.0)	72 (90.0)	0.84	4 (5.2)	9 (11.8)	0.14	0.43	4 (6.3)	9 (14.3)	0.14	0.88
Cumulative Osteoporosis, n (%)*	-	-	-	1 (1.3)	3 (3.85)	0.32	0.90	2 (2.99)	7 (10.5)	0.08	0.75

Data in this table are either expressed as mean ± SD or as median [25-75th percentile]. Adjusted P-values were obtained from multivariable linear and logistic regression analysis considering postoperative clinical, analytical, and densitometric parameters (or its change from baseline) as dependent variables and menopausal status as independent variable, adjusted for age, baseline BMI and type of surgery. *Prevalence of comorbidities is expressed in percentage (%) in each timepoint. Abbreviations: MBS metabolic-bariatric surgery, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, DM2 type 2 diabetes mellitus, HTN hypertension

Discussion

This study aimed to assess the impact of menopause at the time of MBS on changes in cardiometabolic profile, bone mineral density and body composition outcomes in middle-aged women after a two-year follow-up period. Overall, postmenopausal women had a less favourable cardiometabolic profile at baseline, along with elevated FG and HbA1c levels. While MBS improved metabolic outcomes in both groups, postmenopausal patients exhibited a higher reduction in HbA1c over time. Regarding bone health, they had lower preoperative BMD and BMC and experienced a slightly more pronounced postoperative decline, particularly in total femur and total body measurements. Although body composition changes were comparable, postmenopausal women showed a slightly greater reduction in lean mass, particularly in the arms.

Whilst there are some studies that investigate the influence of age on the effectiveness of MBS, few consider the impact of menopausal status on its results [9]. Due to changes in hormonal levels, particularly estrogen deficiency, menopause is associated with a significant increase in fat mass (~ 5–10%), primarily in visceral adipose tissue, which has more deleterious metabolic effects.

Furthermore, menopause is associated with lean body mass loss [14, 15]. However, Greendale Gail A et al. [16] show that these changes in body composition do not lead to any noticeable acceleration in weight gain or BMI at the beginning of the menopausal transition. Furthermore, it is important to mention that the process of aging itself involves a progressive decline in lean muscle mass and a greater tendency to accumulate excess fat, changes that can also be influenced by alterations in dietary intake and reduced physical activity [9].

To address the impact of menopause in weight loss after MBS, it is essential to determine whether menopause directly interferes with the surgery's effects on body weight and metabolic health [15]. In our study, no differences were found between groups regarding weight and BMI at baseline neither in its variation during the follow-up. However, Walędziak Maciej et al. [9] suggest menopause as a key factor influencing anthropometric measures outcomes following MBS, with postmenopausal patients experiencing a lower weight loss, BMI, hip circumference, and waist circumference changes when compared to premenopausal patients [17]. Notably, their study had a significantly lower mean age (39 years) than ours and did not specify participants' baseline BMI, limiting comparability. A lower mean age may indicate a wider age gap between pre- and postmenopausal groups, which could exacerbate differences in body composition changes. Additionally, in our study, even though the analysis was adjusted for the

type of surgery, the higher proportion of RYGB procedures may have mitigated potential disparities, given this surgery's greater efficacy in promoting weight loss and metabolic improvements.

Moreover, our study suggests that postmenopausal women exhibited higher levels of TC, HDL, FG, and HbA1c. In this context, Mendonça F, et al. [17] research on the effects of MBS on cardiometabolic risk in elderly individuals revealed positive outcomes in these patients, with significant weight loss and improvements in glucose and lipid profiles, compared to younger patients. Furthermore, the procedure significantly reduced the prevalence of HTN, T2D, and dyslipidemia, proving to be an effective treatment for this age group. In our study, although postmenopausal patients showed a tendency for higher reductions of HbA1C than premenopausal patients, none of the variables related to remission of comorbidities exhibited differences between groups two years after MBS, further stressing the beneficial metabolic effects regardless of menopausal status.

Although the benefits of MBS are well-documented, there are ongoing concerns regarding its potential adverse effects on the skeletal system, particularly its contribution to bone loss. Xiaodan O. et al. [18] suggest there is a marked decline of femoral neck and lumbar spine BMD in older patients (> 40 years old) following MBS. Luhrs AR et al. [19] disclose a significant decrease in total, spine and right rib BMC and total spine and right rib BMD in postmenopausal women one year after MBS. Moilanen A. et al. [20] unveils that over the 25-year follow-up period, the femoral neck in postmenopausal women underwent a progressive reduction displaying a consistent pattern between the ages of 53.3 and 77.4 years. Consistently, our results show a statistically significant reduction of BMC and BMD of total femur and total body in postmenopausal women. The clinical significance of these slight variations (mainly regarding total femur BMD) is still unknown and requires further investigation in prospective studies with longer follow-up periods, particularly as no differences were observed in the prevalence of osteopenia or osteoporosis between groups in our study. The fact that no association between postmenopausal status and the development of osteopenia or osteoporosis at either 1 or 2 years was observed also reinforces the notion that a two-year follow-up may be insufficient to fully capture the skeletal impact of the perimenopausal transition among women submitted to MBS. Additionally, women exhibited signs of increased bone turnover as early as six months post-surgery. The factors influencing bone metabolism following MBS are multifaceted and likely vary based on the type of procedure performed. Variations in BMC or BMD at specific sites indicate that mechanical load plays a crucial role in preserving bone integrity [19].

Sarcopenic Obesity is a condition that is strongly associated with adverse health outcomes and comorbidities, and the results of our study uncover that SO's prevalence was highly significant (89.5%) in our sample at the time of surgery, without differences between groups. After a two-year follow-up period we noticed that the prevalence of SO decreased substantially with MBS, regardless of menopausal status. These results align with previous studies regarding the impact of MBS on SO outcomes in middle-aged woman, one year after surgery [21]. On the other hand, our results show that osteopenia was more prevalent among postmenopausal women. This scenario primarily results from the hypoestrogenism characteristic of menopause, which enhances bone resorption and diminishes bone formation [22, 23].

Nonetheless, post-MBS weight loss often results in muscle mass reduction, especially among individuals with pre-existing health conditions. Alba DL. et al. [24] suggest that, due to its malabsorptive mechanisms, RYGB led to a 48% fat mass reduction accompanied by a loss of 13% in total lean mass 12 months after the procedure. Notwithstanding, previous research demonstrated that even though MBS leads to inexorable loss in lean mass (10–45%) 12 months after surgery, there is a trend for stabilization or even a slight increase after the 18th month post-RYGB [25–35]. Indeed, Santini S. et al. [14] showed that postmenopausal women exhibit a reduced fat mass percentage and visceral adipose tissue at least two years after MBS, while maintaining lean mass percentage compared to non-operated individuals. Interestingly, our study showed that postmenopausal women experienced a slightly greater decrease in total body and arm lean mass one and two years after surgery. However, although statistically significant, the absolute magnitude of this difference was small (approximately − 0.3 kg) and of uncertain clinical relevance. This interpretation aligns with previous data showing that even older patients (≥ 60 years) do not exhibit a disproportionately greater loss of lean mass following metabolic-bariatric surgery, suggesting that menopausal status may not exert a major independent effect on postoperative lean mass trajectories. Our results were consistent with Luhrs AR et al. [19] considering that these women presented a significant decrease in both lean and fat mass on DXA imaging, as well as a decrease in total, spine and right rib BMC and spine and right rib BMD. Therefore, since postmenopausal individuals who have undergone MBS may exhibit multiple risk factors for lean mass loss and sarcopenia, including low estrogen levels, advanced age, physical inactivity, insufficient protein intake, and vitamin D deficiency, it is important to acknowledge the possible risks of this surgery particularly in this group of patients [35]. Furthermore, it is of paramount importance to protect these patients from metabolic and cardiovascular complications by

improving their body composition [36]. While a reduction in visceral adipose tissue decreases cardiometabolic risk [37], lean mass is inversely related to factors associated with cardiovascular complications [38] and is the primary determinant of basal metabolism, contributing to the long-term preservation of body weight [39].

Limitations of this Study

Our study is subject to several limitations that merit careful consideration. Firstly, the presence of missing information in specific variables, including SBP and waist circumference at baseline (41.4% and 62.4%, respectively) and during follow-up (69.8% missing for SBP variation at the one-year mark and 77.8% at the two-year timepoint) due to telemedicine during COVID-19 pandemic could have decreased the statistical power to analyse these variables. Despite this fact, it was still possible to perform bone densitometry and collect blood samples for laboratory tests in these patients.

Menopausal status was defined at baseline and not reassessed as a time-varying exposure during follow-up. Given the age range of the cohort and the two-year follow-up period, some women initially classified as premenopausal may have transitioned to menopause during follow-up. This may have resulted in non-differential misclassification and potentially attenuated between-group differences in bone and body composition outcomes. Menopausal status was defined based on clinical criteria, and biochemical confirmation with serial measurements of gonadotropins and estradiol was not systematically performed throughout follow-up. Although clinical criteria are widely accepted for menopause diagnosis, particularly in women over 45 years, the absence of systematic biochemical reassessment may have contributed to residual misclassification in women close to the menopausal transition.

Physical activity and nutritional intake (particularly of protein and calcium) were not addressed. Although supplementation was prescribed according to standardized post-bariatric protocols, objective adherence measures were not available. As adherence to calcium, vitamin D, protein, and other supplements may influence bone metabolism and body composition outcomes, residual confounding related to compliance cannot be excluded. Also, the authors did not collect information about functional assessments, that is an also important factor for the definition of sarcopenic obesity. For that reason, we used ALM/W as an approximate surrogate. Wrist bone density was not assessed, which could have provided additional insight, particularly in patients with hyperparathyroidism. Bone-specific alkaline phosphatase was unavailable due to budget constraints and could not be analyzed. Another limitation lies in the fact that thiazide diuretic usage was not evaluated.

Although surgery type was included as an adjustment variable and sensitivity analyses were conducted within the Roux-en-Y gastric bypass subgroup, the study was not specifically designed to provide a direct comparison of bone mineral density changes between Roux-en-Y gastric bypass and sleeve gastrectomy. Therefore, conclusions regarding differential procedure-specific skeletal effects should be interpreted with caution. The study was not specifically powered to evaluate progression to osteoporosis according to surgical procedure type, and procedure-stratified progression analyses should therefore be interpreted with caution.

The observational nature of the study limits the ability to draw conclusions on causal associations. Finally, despite the large number of variables included in the analysis, we cannot exclude residual confounding.

Strengths of this Study

In the present study, we longitudinally assess middle-aged women regarding the impact of menopause at the time of MBS on changes in BMD and body composition, pioneering research in a field that remains largely unexplored. Additionally, the two-year follow-up period and the considerable sample size of our study strengthens its validity and enhances the applicability of our findings. Furthermore, this study relied on DXA as the main evaluation tool, as recommended by the ESPEN and EASO consensus due to its greater accuracy over bioelectrical impedance analysis [13].

Conclusion

This study underscores the influence of menopausal status on BMD and body composition in middle-aged women undergoing MBS. While weight loss and fat mass reduction were comparable between groups, postmenopausal women exhibited a more pronounced decline in total body lean mass and arm lean mass over the two-year follow-up period. Moreover, postmenopausal patients experienced a significant reduction in BMC and total femur BMD, highlighting the increased vulnerability of this group to bone loss.

MBS demonstrated overall benefits in improving body composition and metabolic parameters, including a notable remission of sarcopenic obesity, with these metabolic effects not appearing to be influenced by menopausal status.

Targeted post-surgical management strategies incorporating optimized nutritional support, exercise programs and rigorous bone health monitoring are imperative for postmenopausal patients to mitigate potential adverse effects. Further longitudinal research is warranted to elucidate the long-term impact of MBS in this population and refine clinical interventions accordingly.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11695-026-08565-w.

Author contributions M.M .and F.M.(first co-authors, contributed equally to this work): investigation, supervision, writing - original draft; A.R.L. and J.S.N.– Data curation, formal analysis and visualization, writing – review and editing ; P.S., C.L., I.R., T.M.: investigation, writing – review and editing; J.P., D.F., A.V., A.O., T.F., A.F., S.V., A.N., J.T.G., E.L.C., CRIO: resources, writing – review and editing; R.S. and P. F.: conceptualization, investigation, methodology, resources.

Funding None.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Written informed consent was obtained from all individual participants included in the study.

Competing interests The authors declare no competing interests.

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Supplementary Table 1. Comparative analysis of multivitamin and mineral supplements at baseline, one and two-years after BS

Variable	Baseline				One-year after BS				Two-years after BS			
	Overall	No Menopause (n=82)	Menopause (n=80)	P Value	No Menopause (n=81)	Menopause (n=79)	P Value	Adjusted P value	No Menopause (n=71)	Menopause (n=67)	P value	Adjusted P value
Multivitamin-mineral	0 (0.0)	0 (0.0)	0 (0.0)	-	79 (97.5)	76 (97.4)	0.97	0.86	66 (90.4)	63 (95.5)	0.25	0.19
Vitamin D, n (%)	5 (3.1)	4 (4.9)	1 (1.2)	0.18	29 (36.2)	29 (37.2)	0.9	0.12	25 (34.2)	24 (37.5)	0.69	0.08
Mg, n (%)	2 (1.2)	2 (2.4)	0 (0.0)	0.16	7 (8.6)	9 (11.5)	0.54	0.54	11 (15.1)	10 (15.2)	0.99	0.76
Ca, n (%)	-	-	-	-	1 (1.2)	0 (0.0)	0.32	-	1 (1.4)	0 (0.0)	0.34	-

Abbreviations: Mg magnesium, Ca calcium.

Supplementary Table 2. Comparative analysis of anthropometric parameters, blood pressure, laboratory parameters variation six-months after BS

Variable	Variation six-months after BS			
	No Menopause (n=82)	Menopause (n=80)	P Value	Adjusted P Value
Weight (kg)	-30.1 ± 8.2	-29.1 ± 9.2	0.47	**0.039**
BMI (kg/m^2)	-11.7 ± 3.1	-11.4 ± 3.5	0.57	0.09
SBP (mmHg)	-9.54 ± 17.66	-6.91 ± 16.00	0.59	0.84
DBP (mmHg)	-10.4 ± 18.2	-10.3 ± 15.0	0.99	0.68
Hemoglobin (g/dL)	-0.26 ± 0.78	-0.36 ± 0.96	0.47	0.42
TC (mg/dL)	-22.8 ± 30.1	-19.4 ± 46.6	0.59	0.96
HDL (mg/dL)	-0.92 ± 7.08	-1.64 ± 7.55	0.54	0.27
LDL (mg/dL)	-14.7 ± 25.9	-14.0 ± 41.5	0.89	0.72
TG (mg/dL)	-37.2 ± 69.4	-28.9 ± 48.2	0.39	0.60
FG (mg/dL)	**-3.51 ± 33.12**	**-20.5 ± 40.0**	**0.004**	**0.003**
HbA1C (%)	**-0.34 ± 0.46**	**-0.61 ± 0.87**	**0.020**	**0.050**
Insulin (µU/mL)	-13.5 ± 23.5	-13.9 ± 21.7	0.90	0.12
C-Peptide (ng/mL)	-1.41 ± 1.62	-1.73 ± 1.85	0.25	0.08
Total Calcium Corrected for Albumin (mEq/L)	-0.01 ± 0.19	0.04 ± 0.18	0.06	0.61
P+ (mg/dL)	0.40 ± 0.52	0.39 ± 0.51	0.94	0.68
Mg (mEq/L)	0.03 ± 0.12	0.03 ± 0.11	0.94	0.40
AST (U/L)	0.94 ± 8.90	0.28 ± 10.70	0.68	0.08
ALT (U/L)	-0.54 ± 11.76	-1.49 ± 16.47	0.68	0.24
GGT (U/L)	**-9.73 ± 10.63**	**-11.6 ± 26.0**	0.56	**0.046**
ALP (U/L)	-0.30 ± 16.08	-0.31 ± 19.41	1.00	0.60
Vitamin D (ng/mL)	**4.97 ± 11.83**	**10.2 ± 11.41**	**0.006**	**0.045**
TSH (µUI/mL)	-0.32 ± 0.68	-0.43 ± 1.60	0.57	0.56
T4L (ng/dL)	0.07 ± 0.10	0.07 ± 0.12	0.91	0.74
PTH (pg/mL)	**0.03 ± 22.40**	**-7.86 ± 20.21**	**0.024**	0.21
Beta-CrossLaps (pg/mL)	**0.51 ± 0.21**	**0.63 ± 0.27**	**0.003**	**0.052**
Osteocalcin (ng/mL)	**13.6 ± 7.3**	**18.0 ± 11.8**	**0.009**	**0.089**
Uric Acid (mg/dL)	-0.79 ± 0.84	-0.83 ± 1.24	0.79	0.17
Creatinine (mg/dL)	-0.00 ± 0.10	-0.00 ± 0.10	0.94	0.66
eGFR (mL/min/1.73 m^2)	0.01 ± 10.25	0.70 ± 11.58	0.69	0.48
24H-Urine Ca (mg/kg/24h)	-2.22 ± 4.50	-1.24 ± 4.12	0.21	0.24
Albumin-to-creatinine ratio (mg/g)	-30.7 ± 131.3	-24.2 ± 141.0	0.77	0.63

Data in this table are expressed as mean ± SD. Abbreviations: BS bariatric surgery, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, FG fasting glucose, HbA1c hemoglobin A1c, CT total cholesterol, HDL high-density lipoprotein cholesterol, LDL low-density lipoprotein cholesterol, TG triglycerides, GGT gamma-glutamyltransferase, ALP alkaline phosphatase, AST aspartate aminotransferase, ALT alanine aminotransferase, P+ phosphorus, Ca calcium, Mg magnesium, PTH parathyroid hormone, T4L free thyroxine, TSH thyroid-stimulating hormone.

CHAPTER 4

DISCUSSION

This investigation primarily aimed to clarify the true impact of bariatric surgery (BS) on bone metabolism and body composition, focusing on the two most performed bariatric techniques (Roux-en-Y gastric bypass – RYGB – and Sleeve gastrectomy – SG). One of the main results of our BARIATRIC BONE study was a more pronounced decline in total femur BMD and T-score at one and two years, and in femoral neck BMD and T-score two years after RYGB. In addition, this surgical technique was a predictor of BMD reductions at both hip sites. Our findings are in line with other papers, including those mentioned in the discussion of BARIATRIC BONE study and a recently published secondary analysis of the BARI-LIFESTYLE trial. This study included 39 adults submitted to RYGB and 61 undergoing SG. One year after surgery, there was a reduction in total hip (RYGB -9.8 ± 3.9% *vs* SG -6.5± 3.7%, p<0.001), femoral neck (RYGB -6.7 ± 6.1% *vs* SG -3.3 ± 7.3%, p=0.026) and lumbar spine BMD (-4.5 ± 4.5% *vs* SG -2.0 ± 3.2%, p<0.001)[49]. Globally, these results are particularly important because femoral neck and total hip BMD are considered the best densitometric parameters for predicting hip and major osteoporotic fracture risk, with some evidence suggesting that total hip BMD is slightly superior[50, 51]. Similarly, a recent position statement also presented total femur T-score as the preferential treatment target, since it best reflects subsequent fracture risk at both vertebral and non-vertebral areas in patients on osteoporosis treatment[52]. Taken together, these findings support the results of a retrospective cohort study including 17 971 patients, which showed that patients submitted to restrictive BS suffered fewer proximal hip fractures when compared with those that underwent hypoabsorptive techniques (0.31% *vs* 0.61% for hypoabsorptive procedures, OR 0.508, 95% CI [0.291, 0.920], p=0.021). No differences were found for vertebral fracture or the occurrence of falls, with a higher probability to sustain a fracture more than 3 years after surgery [53]. This is in line with results of a meta-analysis published in 2022, which concluded that the relative risk of any fracture was 61% higher ($p < 0.04$) after hypoabsorptive BS techniques, with a one- to two-fold increased risk of hip fractures compared to restrictive procedures. The risk of fracture appeared to increase at a

mean/median follow-up of more than 2 years[54]. Another meta-analysis published in the same year, showed similar findings regarding the increased risk of fracture after hypoabsorptive techniques[55].

The accumulating evidence regarding adverse skeletal effects after BS has highlighted the importance of their clinical consequences and appropriate management. This culminated in the elaboration of different guidelines addressing the screening, prevention and treatment of osteoporosis secondary to BS[56-58]. The most frequently cited are the 2022 European Calcified Tissue Society guidelines (ECTS) and the 2020 American Society for Metabolism and Bariatric Surgery (ASMBS) guidelines that exhibit slight differences. The American guidelines advocate for the study of 1) all women with 65 or more years and men aged 70+ years, 2) postmenopausal women and men above 50-69 years according to the risk factor profile, and 3) men with 50 or more years with an adult age fracture[56]. In turn, the European guidelines, assessment is recommended in in all menopausal women and men with 50 or more years. Premenopausal women and men with less than 50 years should be evaluated if they present high risk of fracture (fragility fracture after the age of 40, comorbidities or medications associated with osteoporosis)[57]. Both societies endorse the measurement of BMD by Dual-Energy X-Ray Absorptiometry (DEXA) of the hip and lumbar spine, and the assessment of bone turnover markers. In addition, the ECTS guideline also supports the use spine radiographs/ vertebral fracture assessment and the use of FRAX® to predict fracture risk (although acknowledging its limitations in this context). It also stressed the importance of evaluating clinical factors such as the history of fractures, alcohol consumption or smoking habits[59]. The ASMBS guideline do not address criteria for osteoporosis treatment while ECTS guideline advise for treatment among postmenopausal and men with 50 or more years with, at least, one of the following: 1) history of recent fragility fracture (with >40 years), 2) T-score ≤ - 2 at the hip/lumbar spine, 3) FRAX score (including femoral neck BMD) exceeding 3% for hip fracture risk at 10 years and 20% for

major fracture. A retrospective cohort study, conducted between February 2019 to March 2022, evaluated the implementation of the ECTS guideline in men with 50 or more years and in postmenopausal women submitted to BS. It included 170 individuals (84.7% women; median age of 59 years) and 33 of them qualified for antiosteoporosis medication before and after BS, revealing a prevalence of 19.6% in this group. The majority of these 33 individuals fulfilled the European guideline criteria by presenting a BMD T-score of −2 or lower (n=25, 14.7% [CI 95%: 9.7%–20.9%]) and a recent history of fragility fractures (n=12, 7.1% [CI 95%: 3.7%–12.0%])[60]. This study reinforces the importance of a proper bone health evaluation before and after BS among older subjects, considering that a substantial proportion of these patients (nearly one in five) may require bone-strengthening therapy initiation in this context. Treatment indications for younger patients are missing.

The therapeutic approach includes smoking and alcohol cessation, promotion of physical activity (aerobic and strength exercise programs), treatment of vitamin D deficiency and optimization of protein and total daily calcium intake[61]. The ASMBS guideline proposes calcium supplementation with 1200–1500 mg per day after SG and RYGB, together with a minimum vitamin D3 intake of 3000 IU per day (and up to 6000 IU per day), titrated to achieve levels of 25-OH Vitamin D >30 ng/mL[56]. Bone-strengthening therapy includes zoledronic acid as the primary pharmacological option followed by denosumab as a second choice (in cases of contraindication or intolerance to zoledronic acid, considering its risk of rebound effect on treatment discontinuation). Oral bisphosphonates should be avoided due to gastric irritation, potential of anastomotic ulceration, and impaired absorption. Data regarding the efficacy and safety of osteoanabolic agents to treat osteoporosis after BS is missing [57, 59].

Despite scientific community`s initial focus on bone health after BS, increasing attention has been directed during the last decade towards the role of skeletal muscle, lean body mass and body composition changes. Similarly to bone mass, BS is associated with a

significant decline in skeletal muscle mass, a fact that is more notorious in the first 3 months after surgery (about 55% of the mean 8.23Kg lean body mass lost during the first year occurred within this period) according to a recent meta-analysis including 59 studies[62]. In our BARIATRIC BONE study, both groups lost a mean of 6.3Kg of lean body mass one year and 7.4Kg two years after BS. This decline in lean body mass results in mechanical unloading of the skeleton, which is one of the central mechanisms of bone loss after bariatric procedures[63]. This occurs because mechanical loading regulates bone mass, microarchitectural properties and shape in response to different mechanical stimuli exerted on it. Skeletal muscle activity is the primary source of mechanical load on bone via tensile (muscle contraction), bending (seen in long bones, such as in cases when an object distal to the limb is lifted) and compressive forces (contraction of the muscle across joints)[64]. Several theories have been proposed to explain the impact of muscle mass on bone, such as the Frost's mechanostat theory. It states that when mechanical stimuli surpass a certain threshold, bone formation is favored to increase resistance and stiffness against excessive forces. In contrast, if stimuli are below this threshold, bone mass is lost in a site-specific manner due to bone resorption for greater body efficiency[65]. This theory is supported by low mechanical loading models such as immobilization or prolonged bed rest, zero gravity in space missions, presenting harmful effects not only on bone but also on muscle itself[64]. Bone adaptation to mechanical loading is dependent on the capacity of bone cells to perceive mechanical stimuli and then convert them into a series of structural and biochemical responses [66]. This biochemical bone-muscle crosstalk is bidirectional and can also present systemic effects on distant tissues or organs, which highlights the role of skeletal muscle as the largest endocrine organ in the human body[67]. Muscle fibers release cytokines and other peptides called myokines that, in addition to bone formation, also influence several biological processes such as cognitive mechanisms, lipid and glucose homeostasis, browning of white adipose tissue, endothelial cell function, tumor growth, hypertrophy and skin structure[24]. These myokines secreted by the contracting muscle include

myostatin, insulin-like growth factors (IGF-1), irisin, β-aminoisobutyric acid, brain derived neurotropic factor, IL-6, IL-7, IL-15, among others[68]. Considering the close relationship between muscle and bone, all these agents are being studied as putative targets not only to regulate muscle mass but also bone mass[64]. A recently discovered myokine is Fibroblast Growth Factor-21 (FGF-21). Despite being predominantly produced in liver and adipose tissue under basal conditions, its levels are increased in conditions of mitochondrial dysfunction, muscular dystrophy and exercise. Studies to date support the notion that this myokine may allow or mediate muscle wasting in processes associated with muscle atrophy[69]. Despite this fact, data regarding its levels after BS or its role in bone/muscle metabolism in this context is scarce. This thesis presents the first study to address the influence of FGF-21 and also Fibroblast Growth Factor-23 (FGF-23) levels in bone mineral density according to bariatric surgery technique. FGF-21 was frequently below the assay's detection limit, particularly among patients who underwent sleeve gastrectomy, whereas baseline FGF-23 levels were higher in this group. Neither hormone predicted two-year BMD changes at the lumbar spine, total femur or femoral neck. These findings do not support FGF-21 or FGF-23 as predictors of postoperative BMD variation in this cohort but address an underexplored endocrine dimension of skeletal changes after bariatric surgery.

Considering these interconnections and their clinical impact on patients, the observed loss of muscle mass after BS have raised concerns about sarcopenia, a concept that refers to a muscle disease characterized by low muscle mass, strength and/or physical performance. This progressive and systemic disorder may occur at any age, being associated with a higher risk of adverse outcomes including falls, fractures, functional decline and mortality[70]. A recent study applying the European Working Group on Sarcopenia in Older People (EWGSOP2) criteria for the diagnosis of sarcopenia (reduced strength assessed by handgrip test and/or reduced muscle mass evaluated by diminished appendicular skeletal muscle mass/height^2) and its proposed cut-offs,

showed that 35% of the individuals had probable sarcopenia previously to BS, with none of them presenting both criteria for achieving the diagnosis. One month after BS the result was similar. After that timepoint, 11.8% patients at six and 29.4% at twelve months after BS presented both criteria for a diagnosis of sarcopenia, while at eighteen months after surgery this proportion increased to 52.9%[71]. In our BARIATRIC BONE study, RYGB was associated with greater reductions in total, trunk and legs fat mass; however lean mass loss was similar after both surgical techniques (6.3Kg one year and 7.4Kg two years after BS). This lean mass loss observed in the RYGB group (approximately 18% of the total weight loss of 41Kg) is slightly lower than the range of 20-35% reported in other papers using DEXA to evaluate body composition after RYGB. Interestingly, unlike our study, the limited available literature has not documented significant differences between RYGB and SG in body composition variation after BS (either in the short- or long term)[4].

A more recent concept than sarcopenia is sarcopenic obesity (SO), defined by the coexistence of low muscle mass and function (sarcopenia) with excessive adiposity (especially visceral fat). It is known that obesity and sarcopenia are defined by a low grade pro-inflammatory state which affects several metabolic mechanisms, contributing to the disruption of the normal functions of skeletal muscle and adipose tissue. SO is also linked with several other disorders such as oxidative stress, mitochondrial dysfunction, and insulin resistance[72].The association of all these processes with adipokine dysregulation, creates a synergistic environment that further compromises muscle quality and bone metabolism, which amplifies the risk of osteoporosis, bone fractures, cardiometabolic disease, disability, and mortality, in a way that surpasses what is seen in obesity or sarcopenia alone[72-74]. In an effort to uniformize the definition and diagnostic criteria of SO, the ESPEN and the EASO published recently a consensus statement. According to this document, SO screening relies on high body mass index or waist circumference together with surrogate markers of sarcopenia (such as clinical

symptoms of risk factors including chronic disease diagnosis, repeated falls, weakness, among others) or validated questionnaires (such as the SARC-F). After a positive screening, the diagnosis is performed in two steps evaluated sequentially. First, skeletal muscle functional parameters are assessed (e.g. hand grip strength or chair stand test). If a low muscle function is detected, body composition should be evaluated with dual-energy X-ray absorptiometry (DEXA) or bioelectrical impedance analysis. The diagnosis of SO is established only when both altered muscle function and body composition coexist[28]. SO may arise during the initial months after BS but muscle loss and low muscle mass within this stage are not invariably associated with worse functional outcomes, considering that some patients can improve muscle performance. SO seems to present a more important issue in the later phases after BS, such as in cases of weight regain. This occurs because most of the regained weight consists of adipose tissue, in patients who have already experienced substantial muscle loss in the initial stages after BS[29, 75]. One of the studies included in this thesis aimed at studying the impact of bariatric surgery on sarcopenic obesity outcomes. Despite not evaluating muscle strength, this investigation divided the 140 included patients into tertiles according to the severity of lean mass reduction evaluated by DEXA adjusted to body weight (W). A diagnosis of SO was considered when the sum of the lean mass of arms and legs - appendicular lean mass (ALM) - adjusted to W was < 23.47% (according to the cutoffs from the ESPEN/EASO guidelines). Interestingly, BS induced a drastic reduction of overall SO prevalence from 89.3% before surgery to 2.9% after surgery. A recent systematic review found a highly heterogenous prevalence of SO in the 12 studies included, that ranged from 0 to 89.3% before BS, with a maximum prevalence of 57% six months after surgery and 35.7% ten or more years after BS (overall BS prevalence after BS ranged from 0 to 57%). This was explained by differences in diagnostic criteria, methods used to assess body composition and evaluated timepoints [29].

Our study also showed that the group presenting the worst body composition with SO, despite presenting more weight loss, BMI reduction and fat mass, it was the one that presented the smaller absolute reduction of lean mass (albeit not statistically significant). This group was the one that also presented the greatest proportion of diabetes (75%) and dyslipidemia (52.8%) remission. The authors concluded that health benefits of BS in SO outcomes and weight reduction are driven mainly by the loss of adipose tissue mass alone rather than significant lean mass compromise[76]. BS has been associated in several systematic reviews with lower grip strength and muscle strength (mainly in the lower limbs), with losses in line with the magnitude of weight reduction. Nonetheless, after adjustment of the muscle strength reduction for lean mass or body weight, no significant changes are seen, with some studies even reporting improvements (including in patients with worse functional status before BS)[77]. Taken together, these findings raise the novel proposition that BS may be an effective therapeutic pillar in the management of SO, alongside exercise interventions (mainly favoring resistance training), high protein intake, calcium and vitamin D supplementation, GLP-1 agonists, among others[78, 79].

This thesis also addressed the prevalence of secondary hyperparathyroidism (SHPT) before and after bariatric surgery. SHPT is an issue commonly associated with decreased BMD and increased risk of fracture[80]. Our retrospective study of 1431 patients concluded that the overall prevalence of SHPT was 24.9% before surgery (23.7 before SG and 25.5% before RYGB). One year after BS, the prevalence was 12.8% in the RYGB group and 5.3% in the SG group, increasing to 27.0% and 6.9%, respectively, four years after surgery. Interestingly, the only independent predictor of SHPT four years after BS was RYGB. This study was later included in a meta-analysis including 9 studies with a total of 5585 patients that showed a marked increase in SHPT among patients submitted to gastric bypass at the 2-year and long-term follow-up intervals with no significant differences in the first two years after BS[81]. In contrast to the results of our

retrospective study and of the meta-analysis, the BARIATRIC BONE study showed no statistically significant differences between surgical procedures regarding the variation of parathyroid hormone (PTH) levels one and two years after BS. These differences may be explained, at least in part, by the shorter follow-up of two years of the prospective study and differential vitamin D supplementation rates (e.g., one year after RYGB, 40.4% of the prospective cohort received Vitamin D supplementation *vs* only 20.7% in the retrospective study). In addition, despite the absence of differences in PTH variation between groups after BS in our BARIATRIC BONE study, there was a greater BMD reduction in the hip area among the patients submitted to gastric bypass. Although mechanical factors could play a role, our study demonstrated that absolute lean mass loss after BS was similar between groups (with RYGB group losing proportionally less lean mass due to greater overall weight loss), suggesting that mechanical factors alone cannot fully explain the increased BMD loss after RYGB. This notion is supported by an investigation on BMD at least 10 years after RYGB showing lower bone densities at the hip, tibia, and radius when compared to BMI-matched controls[82]. The fact that BMD loss persists after weight loss stabilization is also another argument to validate this idea[83]. Ultimately, the results of these studies suggest an important role for other players such as gastrointestinal hormones and adipokines, estrogen, inflammatory markers or even the microbiome, as putative drivers for steeper BMD reduction after RYGB[84-87]. As an example, leptin levels rise in states of increased adiposity while the opposite occurs with adiponectin levels[88]. These adipokines seem to have different effects on bone, with leptin presenting an overall positive effect on bone while the role of adiponectin is controversial[32]. A recent systematic review concluded that leptin levels are associated with increased BMD at the lumbar spine and femoral neck with the opposite occurring with adiponectin levels[89]. In addition, a clinical trial found that leptin level presented a greater reduction while adiponectin level exhibited a more pronounced increase after RYGB when compared to SG ($P < 0.05$)[90]. In the BARIATRIC BONE study, patients submitted to RYGB were the ones who lost the greater amount of total

body fat mass, the same happening in the trunk and legs. Considering all this data and the presented associations of leptin and adiponectin with adiposity, it becomes clear that these adipokines can be part of the explanation for the greater hip BMD reduction after RYGB in the BARIATRIC BONE study. Interestingly, our study also showed an increase in total protein levels after SG and a decrease after RYGB (0.63±16.04 *vs* -3.99±4.67g/L, p=0.014), which also occurred with albumin levels (0.54±2.91 *vs* -0.70±2.78g/L, p=0.012, unpublished data). This raises issues regarding nutritional factors, namely the protein intake of patients submitted to RYGB, a fact that becomes more relevant considering that there seems to be a positive association between dietary protein intake and BMD (despite being a complex and non-linear relationship)[91]. An umbrella review of systematic reviews also showed that high protein intake may contribute to reduced hip fracture risk when compared to low protein intake[92], that was precisely the area that presented greater BMD reductions after RYGB in our prospective study. Interestingly, this did not seem to have an impact on lean mass variation as presented above.

Finally, this project also evaluated the impact of menopausal status on bone metabolism and body composition after BS. Two years after surgery, postmenopausal patients presented a steeper decrease in bone mineral content and a greater loss of total femur BMD and whole-body BMD. These findings are in line with the limited available data regarding this issue, that shows that postmenopausal status seems to be associated with greater bone loss and with a more accentuated worsening of bone microarchitecture when compared with premenopausal women or men[93, 94]. In our study, postmenopausal women also showed a slightly greater reduction in total body lean mass and arms lean mass. Hormonal variations associated with aging influence muscle and adipose tissue, with muscle fibers shown to possess estrogen receptors. The fall of estrogen levels after menopause leads to increased visceral fat and impaired muscle mass and strength[95, 96], which can explain, at least partially, the results of our study regarding body composition.

CHAPTER 5

CONCLUSIONS AND FUTURE PERSPECTIVES

This thesis provides evidence supporting the following conclusions:

1. **Roux-en-Y gastric bypass (RYGB) results in greater bone density reductions than sleeve gastrectomy (SG) at both one and two years after surgery.** These differences are observed mainly in the hip: in the total hip BMD at one-year and in both total hip and femoral neck bone mineral density (BMD) at two years after bariatric surgery (BS). RYGB is a predictor of total hip and femoral neck BMD two years after surgery. Baseline BMD (lumbar spine, total hip or femoral neck) is predictor of osteopenia/osteoporosis 2 years after surgery.

2. **RYGB leads to greater weight loss, with steeper reductions in total fat mass and in the proportion of trunk and legs fat mass. Total and regional lean mass loss after RYGB are similar to that seen after SG. RYGB results in greater reduction in bone mineral content when compared with SG.** All these facts are observed both one and two years after bariatric surgery.

3. **Osteocalcin and CTX increase at both one and two years after surgery, with a significantly higher increase in RYGB group. There are no differences between RYGB and SG regarding fracture risk evaluated by FRAX® at both one and two years after surgery**. Calcium collected in 24-urine presents a slight increase after SG and a decrease after RYGB in both timepoints (raising issues about the efficacy of calcium and vitamin D supplementation).

4. **FGF-21 and FGF23 did not predict BMD variations in lumbar spine, total femur and femoral neck after bariatric surgery.** No statistically significant differences were seen globally between surgical techniques in the variation of these two hormones. These results suggest that FGF-21 and FGF-23 are unlikely to explain the observed bone-density changes over the first two years after surgery, while highlighting the need to investigate other endocrine and metabolic pathways that may contribute to skeletal outcomes.

5. **The prevalence of secondary hyperparathyroidism (SHPT) is higher before and 4 years after BS than 1 year after surgery.** The overall prevalence of SHPT raises again some questions about the efficacy of the implemented follow-up plans of calcium and vitamin D supplementation).

6. **Before surgery, SHPT was more prevalent in women than in men, and patients with SHPT presented greater body mass index, lower baseline total calcium, phosphorus and vitamin D levels. One year after surgery, patients with SHPT were older, with higher BMI, with a lower percentage of weight lost. These patients also presented with higher blood pressure, the same happening with plasmatic glucose and HbA1c.** No differences were found before surgery regarding age, systolic, or diastolic blood pressure, glycemic status, ALK-P or CRP (between those with and without SHPT).

7. **Higher body mass index, age, decreased levels of vitamin D and RYGB seem to be independent predictors of SHPT 1 year after surgery. The only independent predictor of SHPT 4 years after surgery was RYGB.**

8. **Despite concerns about hypoabsorptive mechanisms potentially worsening muscle loss, patients with the most severe sarcopenic obesity (SO) undergoing BS lost more fat mass while experiencing the smallest reduction in total skeletal muscle mass.** Remission rates for comorbidities following BS were notable among all groups. SO prevalence in the overall sample was 89.3% in baseline, decreasing to 2.9% one year after BS. Engagement in physical exercise of any kind has increased post-BS (33.1% vs 79.1%).

9. **Two years after BS, postmenopausal patients revealed to have a steeper decrease in bone mineral content, a higher loss of total femur and whole-body bone mineral density. Postmenopausal patients presented a greater**

decrease in total body lean mass and arms lean mass. Postmenopausal patients present a higher prevalence of T2D, hypertension and osteopenia.

Final remarks and future perspectives

Globally, this thesis encompasses the greatest prospective cohort to date comparing the impact of RYGB and SG on bone metabolism with evaluation of BMD and body composition by DEXA, and with measurements of bone metabolism markers two years after surgery. It adds to the literature by validating previous preliminary data on the most deleterious effect of RYGB (depicted as a relevant future topic in the 2022 ECTS position statement[61]) and reinforcing the importance of proper calcium and vitamin D supplementation of bariatric patients. Our article regarding SHPT prevalence also stresses this necessity for proper long-term supplementation, that gains even more relevance after RYGB (give its hypoabsorptive nature). The investigation regarding the impact of menopause status on bone and body composition after BS is among the first studies to address its role on bone health. It is also the first, to our knowledge, to compare the body composition of premenopausal and postmenopausal women after BS, paving the way to other studies in the area. The paper addressing sarcopenic obesity also pioneers in this topic by applying the criteria of the recent ESPEN/EASO guidelines[28].

Future research should include prospective evaluation of bone health and body composition with longer follow-up periods after BS. For that reason, our group will continue to evaluate the BARIATRIC BONE cohort for up to 10 years after surgery. The use of tools to evaluate bone microarchitecture such as the Trabecular Bone Score can add valuable information in this context. Similarly, the assessment of putative mediators such as GLP-1, GLP-2, GIP and irisin may further enhance understanding of bone health after BS. Considering the sarcopenic obesity issue, further investigation incorporating

not only evaluation of body composition of the new criteria but also measurements of muscle strength is needed to clarify this condition after surgery.

CHAPTER 6

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